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Monthly Message

The Office of the Assistant Secretary of Defense (Health and Medical) was reorganized in 1959 and responsibilities distinctly stated in the new charter:

> The Assistant Secretary of Defense (Health and Medical) is the principal staff assistant to the Secretary of Defense in the following functional fields:
>
> 1. Health and sanitation;
> 2. Medical care and treatment of patients;
> 3. Hospitals and related health and medical facilities;
> 4. Health and medical personnel.

Then follows an elaboration of each of these responsibilities.

The primary function of the Office is to plan for and promote policies that will provide for the best military medical establishment possible with two primary aims: first, in war; second, during peace. As you can readily see this is vastly more inclusive than simple hospital care with large hospital systems and medical educational and training programs. During peace-time purely from a professional care standpoint the military medical departments are responsible for approximately 2,500,000 active members of the armed forces, about 3,000,000 dependents, and a large group of retired personnel with their dependents, perhaps another 2,000,000. Here our difficulties are chiefly those of providing high quality care and sufficient beds. Strangely enough, with the decrease in the numbers of active military personnel, the immediate dependents have increased by about 500,000 because of an older and more stable group in the services with resultant increase of marriages and larger families. Coincidentally there has been considerable fear on the part of the public that due to these pressures there would be an increased building program and demand for more medical and dental officers. So far, however, this has not proved to be the case.

Next month we will speak of military medicine.

Frank B. Berry

FRANK B. BERRY, M.D.
Assistant Secretary of Defense
(Health and Medical)

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NOTICE TO READERS

The Editors regret to announce that the *United States Armed Forces Medical Journal* will cease publication with the December 1960 issue, completing volume 11.

As many as possible of the backlog of accepted articles will be published in the remaining issues. Manuscripts for which space cannot be found will be returned to the authors. No additional articles can be accepted.

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UNITED STATES

Armed Forces Medical Journal

Fluoridation of Water for Dental Public Health

COLONEL KENNETH R. ELWELL, USAF, DC

DENTAL CARIES, our most prevalent disease, remains unconquered.[1] Fluoridation of public water supplies is now available for the mass control of this disease that affects the health, comfort, and appearance of almost every person throughout his lifetime. Before its introduction and acceptance, fluoridation had more years of scientific study and proof than any other public health measure.[2] Authoritative long-term investigations [3–5] have established that fluoridation is effective, practical, and safe. Fluoridation today is the best available means of applying sound preventive measures to the overwhelming public health problem of tooth decay.

FLUORIDATION OF WATER SUPPLIES

Fluoridation is simply the controlled adjustment of the amount of fluorides in public drinking water supplies to provide approximately 1 part per million (1 ppm) of fluoride. In areas where drinking waters naturally contain fluorides in excess of 1 ppm, downward adjustment of the fluoride, or partial defluoridation, is required to reach the optimal concentration. Too much fluoride in drinking water results in the condition known as dental fluorosis or mottled enamel, whereas too little fluoride is associated with a high incidence of dental caries. Between these two extremes lies the optimal concentration of about 1 ppm, which effectively prevents a substantial amount of dental caries without causing dental fluorosis.[6]

Effectiveness

The favorable evidence for fluoridation is both voluminous and con-

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From Office of the Dental Surgeon, PACAF Base Command, APO 953, San Francisco, Calif. Presented on 28 Nov. 1959 at the Ninth Medical Conference, Camp John Hay, Baguio, Philippine Islands, and on 27 May 1960 at the 52d Annual Convention, Philippine Dental Association, Manila, P.I.

clusive. Dean and his associates [7–9] conducted classic epidemiologic studies on more than 7,000 children between the ages of 12 and 14, who were natives of 21 cities where community drinking waters contained from 0.0 to as much as 2.6 ppm of fluoride. These studies proved that dental caries was reduced by fluorides and that caries could be inhibited at fluoride concentrations too low to cause objectionable mottling of the teeth.

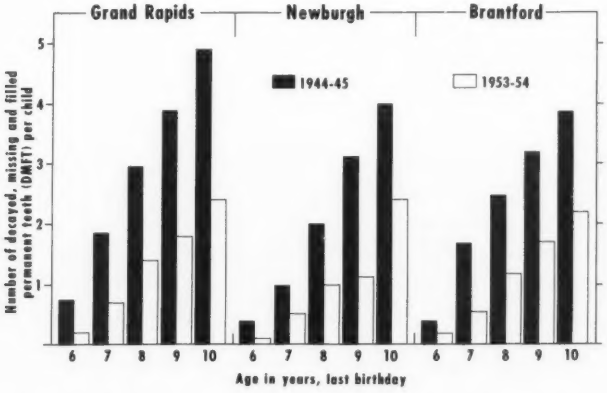

Figure 1. Comparison of prevalence of dental caries in children continuously resident in 3 communities before fluoridation and after 9 years of fluoridation. (From Dean [4])

Each of a series of well-controlled field studies by public health research personnel was conducted for over 10 years at Grand Rapids, Michigan,[10,11] Newburgh, New York,[12] Brantford, Ontario,[13] Evanston, Illinois,[14] and in other areas [15] (figs. 1 and 2). The published results of these studies gave direct and positive evidence that controlled fluoridation of drinking water is consistently effective in reducing tooth decay in children by as much as 60 percent. It is of special interest to note that at Grand Rapids dental decay in 6- to 10-year old children dropped 76, 62, 52, 53, and 51 percent respectively; at Newburgh, the reduction for the same age groups was 77, 53, 51, 64, and 41 percent respectively; and at Brantford the reduction was 65, 66, 52, 47, and 43 percent respectively. Such findings offer direct evidence that tooth decay can be largely controlled through fluoridation of the public water supply.[4] Scientific research has also shown that the known caries-inhibitory effects of fluorides are not dissipated in childhood but continue through adulthood up to at least the age of 44 in persons who continue

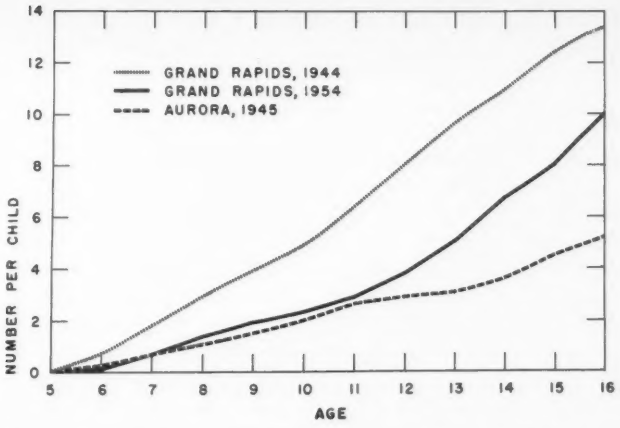

Figure 2. Reduced prevalence of caries in Grand Rapids after 10 years of water fluoridation. (From Arnold, Dean, Jay and Knutson [10])

to use fluoride-bearing water [16,17] (figs. 3 and 4). Unquestionably, fluoridation is highly effective.

Safety

In this connection Leone,[19] chief medical investigator for the National Institute of Dental Research, stated that "we know without question or doubt, that one part per million fluoride in a water supply is absolutely safe, is beneficial and is not productive of any undesirable systemic effect in man." Furthermore, the Inter-Association Committee on Health,[6] which includes the American Dental Association, the American Medical Association, the American Public Health Association, the American Hospital Association, the American Nursing Association, and the American Public Welfare Association, has stated that "accumulated experience provides no evidence that prolonged ingestion of fluorides below the level causing dental fluorosis has any harmful effect." Moreover, based on reports of several conclusive 10-year studies, there is positive evidence that "no clinically significant physiological or functional effects resulted from prolonged ingestion of water containing excessive fluoride (8.0 ppm), except for dental fluorosis." [19] These studies indicate the wide range of general safety, since even up to 8 times the ideal concentration is well tolerated by adults and children with no harmful effect except for dental fluorosis. Fluorosis does not occur at the trace concentrations of about 1.0 ppm recommended

for use in drinking water. Fluoridation, in addition to its consistent effectiveness in reducing future dental decay 60 to 65 percent,[10–15] is nontoxic and completely safe.

Engineering and Technical Feasibility

Fluoride feeder equipment is simple and inexpensive to install, use, and maintain. Equipment in daily operation at waterworks and industrial plants permits the addition of fluoride to any water supply. Engineers and other regular operating personnel of the waterworks have only to install and then to operate standard fluoride feeders as a part of their regular duties. The usual careful handling of the chemical and regular testing of fluoride concentrations are required as routine safeguards. Technically the process of water fluoridation is quite a simple matter for experienced personnel.[20–24] The optimal fluoride concentration for a local water supply has been reported in classic studies by Galagan and Vermillion.[25] The mean maximum temperature for the locality is obtained from the U.S. Weather Bureau covering a period of 5 years or more. Optimal fluoride concentration is correlated with this mean maximum temperature. Table 1 shows the optimal fluoride levels for temperature ranges of 50° F through 90.5° F. Complex individual calculations for each community are not required.[25]

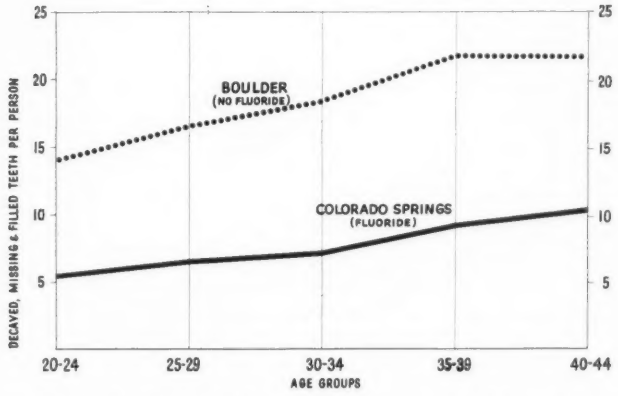

Figure 3. Incidence of decayed, missing, and filled teeth per adult in communities with and without water fluoridation. (From Russell and Elvove [18])

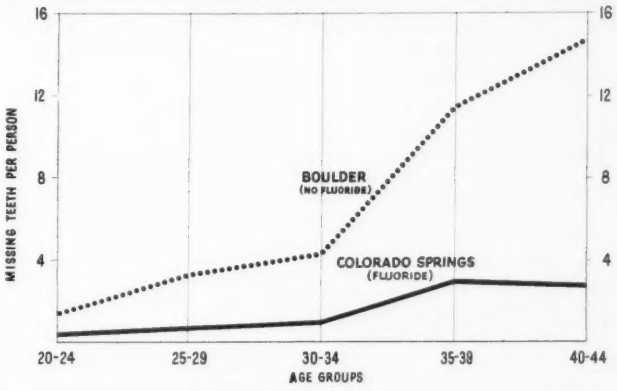

Figure 4. Missing teeth per adult in 2 communities with and without water fluoridation. (From Russell and Elvove [18])

Costs

Fluoridation is really an inexpensive approach to dental public health. Selection of equipment is based upon the type of fluoride to be added to the water supply. Fluorides may be fed either dry or in solution. Larger installations often use economic gravimetric dry feeders costing about $2,000, depending on size and accessories. Volumetric dry feeders and solution feeders are available for use in smaller installations at even less cost.[5]

The fluoride chemical to be used in the feeders also costs very little. For example, for sodium fluoride the average per capita cost has been estimated at only 12 to 14 cents a year.[5] The American

Table 1. *Optimal fluoride concentrations at various environmental temperatures**

Mean maximum temperature (degrees F)	*Fluoride concentration (ppm)*
50.0–53.7	1.2
53.8–58.3	1.1
58.4–63.8	1.0
63.9–70.6	0.9
70.7–79.2	0.8
79.3–90.5	0.7

* From Galagan and Vermillion.[25]

Dental Association [26] has stated that the cost of fluoridation averages less than 9 cents per person per year, or often less than the cost of a single candy bar. The Association [26] also cites the interesting fact that the cost of a single average filling will pay for fluoride for 1 person for about 30 years.

ALTERNATIVES TO COMMUNAL FLUORIDATION

How do alternative methods compare in value to fluoridation? Many communities, unable to fluoridate their public water supplies, need answers to these questions in order to evaluate the possible benefits of the available substitutes.

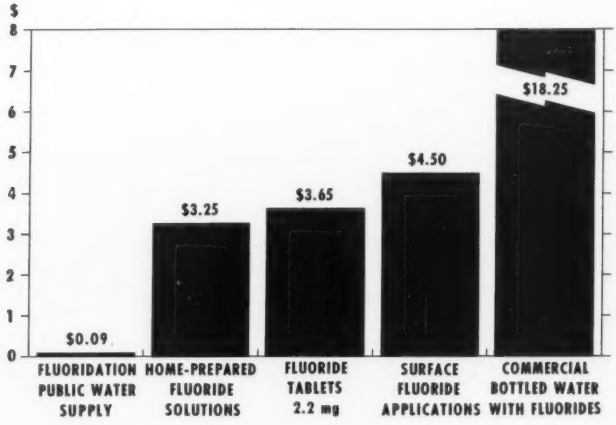

Figure 5. Comparative per capita annual costs of alternative methods of using fluorides to reduce tooth decay.

The two major methods of obtaining fluorides are (1) ingestion of fluoridated water or fluoride dietary supplements and (2) the application of fluoride solutions to tooth surfaces. Fluoridated communal water is by far the method of choice, because of its superior effectiveness, assured safety, maximum convenience, and extremely low cost. Despite certain disadvantages, however, substitute methods do offer some of the benefits of fluorides.

Commercially bottled water or home-prepared fluoridated water for infants and children under 2 years of age and fluoride tablets

for children over 2 years of age offer effective means of reducing the incidence of caries. Successful results by these methods, however, require the mother's intelligent and conscientious daily interest and participation over a long period beginning before childbirth and continuing until her child reaches 8-10 years of age.[27] Approximate annual costs of each dietary supplement method are shown in figure 5. Potential hazards exist: improper storage of tablets could result in accidental poisoning of children, and misuse of the tablets over a long period of time could result in fluorosis, especially where the communal drinking water contains a significant fluoride concentration.[27] Safeguards and professional supervision are essential in public use of dietary fluorides. Fluorides in foodstuffs such as milk, bread, salt, and baby foods remain relatively untested and unproved.[28–31] Troches,[32–33] mouth washes,[33–35] and dentifrices [36] containing *sodium* fluoride have been tried without success. It has been reported that dentifrices containing *stannous* fluoride decrease the incidence of caries in children by 35.0 to 50.6 percent [37–39] and in college students by 41.6 percent.[40]

Topical solutions of sodium fluoride reduce the incidence of caries by about 40 percent.[41] *Stannous fluoride solutions appear to be much more effective than sodium fluoride when all reported studies are evaluated.*[42] In a study on primary teeth, McDonald and Muhler [43] reported stannous fluoride to be significantly more effective than sodium fluoride, with differences of 21 to 57 percent in DMFT (decayed, missing, and filled teeth) and 12 to 37 percent in DMFS (decayed, missing, and filled surfaces).

Of utmost interest is Muhler's [44] study, in which topically applied *stannous* fluoride was used on 500 Indiana University students, aged 18 to 35. A single application of 10 percent stannous fluoride resulted in a 24 percent decrease in the DMFT and a 16 percent decrease in the DMFS. This newly developed preventive measure to reduce the incidence of caries has been made a part of the U.S. Air Force preventive dentistry program. Most authorities believe adults derive little, if any, benefit from topical applications of *sodium* fluoride.[42]

Disadvantages of the topical or surface fluoride method are: (1) the limited number of professional and auxiliary personnel available to implement the program, and (2) the relatively high expense, estimated at about $4.50 per child [28] for each series of treatments. Time, money, skilled personnel, and conscientious cooperation are essential to the success of a topical fluoride program.

Briefly summarized, fluoridation of public water supplies is best. Where this method cannot be used, alternative methods with recognized disadvantages may be necessary.

STATUS OF FLUORIDATION

In June 1959, the U.S. Public Health Service [45] estimated that about 42 million Americans in more than 3,500 communities were drinking water with about the ideal amount of fluoride and at a cost of about 9 cents per person per year. Four million residents of the United States drink water that for many years has contained adequate or higher levels of fluoride as a naturally occurring and incidental constituent of local drinking waters.[46]

Health Organizations Endorsing Fluoridation

The American Dental Association [47] has published a list of over 40 national organizations that have adopted policies favorable to fluoridation. In addition to the American Dental Association, these organizations include the American Medical Association, the National Research Council, the U.S. Public Health Service, the National Institutes of Health, the American Waterworks Association, and every other major scientific and professional health organization in the United States, as well as the Department of Defense. The World Health Organization, representing the United States and numerous foreign countries, has also endorsed fluoridation.[3]

Possibly the authoritative endorsement of the American Medical Association,[48–50] first made in 1951 and reaffirmed following a second study in 1957, will be of the greatest interest to professional medical practitioners. These policy statements by the American Association concluded: "Fluoridation of water supplies in a concentration not exceeding one part per million is non-toxic and its principle is endorsed." The American Medical Association also approved a statement of the Inter-Association Committee on Health,[6] of which it is a member, which reads: "Resolved, that the Inter-Association Committee on Health urges the fluoridation of the fluoride-deficient public water supplies of this country as rapidly as plans can be approved by the medical, dental and health department officials and the state departments of health."

Opposition to Fluoridation

It is significant that no recognized national scientific organization, association, or group concerned with health is on record as opposed to the fluoridation of public water supplies.[51] A small number of individual members of the medical, dental, and chemical professions are opposed to fluoridation. Usually these individuals do not question the effectiveness of the measure but raise hypothetic objections to

the toxicity of fluorides. These individuals are gradually accepting the facts about fluoridation.[28, 51]

By far the larger, more vocal group has been composed of persons totally unconcerned with scientific opinions. They form organizations with names such as the Citizens Committee Against Fluoridation and the Pure Water Committee. These committees include drugless healers, naturopaths, chiropractors, food faddists, and scare pamphleteers. These antifluoridationists have advanced fantastic, irresponsible, irrelevant and often false statements involving politics, prejudice, and pseudoscience.[28, 51]

In 1957 over 240 of these statements, claims, and criticisms were classified and appraised in relation to scientific facts as published in the literature.[52] Detailed and voluminous scientific evidence was cited that clearly indicated that fluoridation is practical, safe, and effective, and the method of choice for reducing dental caries. The evidence presented refutes the unfounded opinions and biased assumptions of opponents of fluoridation. Numerous long-term scientific studies confirm the value of fluoridation, whereas there is a complete lack of evidence or of studies of any kind to support the statements of the opponents of fluoridation. It is a simple fact that the evidence overwhelmingly supports fluoridation as a valuable public health measure.

SUGGESTIONS FOR THE HEALTH PROFESSIONS

Civilian medical and dental societies *can* and *should* help their communities to achieve the benefits of a fluoridation program by (1) stimulating interest in a local program, (2) providing information, and (3) enlisting civic groups to serve as leaders.[53]

Military members of the health fields should take direct action to carry out the Department of Defense endorsement of fluoridation and to establish fluoridation of military base water supplies wherever needed. Procedures for the establishment of fluoridation at U.S. bases are relatively simple. Only the following basic requirements are involved: (1) A request must be submitted to the surgeon general of the military department concerned, based on coordinated and comprehensive local surveys that evaluate need, technical and economic feasibility, and related factors. (2) Upon approval of the request, a local project is then established to install, supply, operate, and maintain an efficient water fluoridation program.

Members of the health and allied professions throughout the world should develop an expert knowledge of basic facts about fluoridation to qualify them to counsel laymen. They should also maintain an

active long-term personal interest in the establishment and efficient operation of local fluoridation programs. Every member of the health profession must accept the challenge of providing leadership, authoritative scientific knowledge, and stimulation of action essential to ensure adoption and maximum use of fluorides. Fluorides offer dental public health at a bargain.

SUMMARY

Dental caries is the most prevalent of the chronic diseases, because virtually every person falls victim to it, usually early in life. Fluoridation of community water supplies is the most potent of all measures available for the mass control of dental caries and consistently reduces its incidence by as much as 65 percent.

The fluoridation of water has had more years of scientific testing and evaluation by the public health, dental, medical, and chemical professions than any other public health measure. Several studies covered periods longer than 10 years. About 42 million Americans in more than 3,500 communities (about 1 of every 4 persons) are drinking water containing approximately the ideal fluoride concentration at a per capita cost of about 9 cents a year. The results of all types of investigations have shown that fluoridation is effective, safe, practical, and economical, and is superior to and much less costly than other means of obtaining fluorides. However, despite the disadvantages of alternative means of using fluorides these substitutes should be considered when it is not possible to fluoridate central public water supplies.

Fluoridation of communal water supplies is fully endorsed by every major professional and scientific health organization in the United States. The small but extremely vocal group of opponents of fluoridation have been long on opinions but short on evidence to support their views. Careful evaluations of each objection or claim, in relationship to long-term research results, reveal that the sound and acceptable evidence consistently supports fluoridation.

It is suggested that wherever local drinking waters lack sufficient fluorides to protect oral health, the health profession can and should respond to the challenging needs for positive leadership, knowledge, and action to bring the recognized benefits of fluoridation to their local communities.

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Isolation-Perfusion Technic in Cancer Chemotherapy

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THE ISOLATION-PERFUSION TECHNIC for the treatment of cancer was introduced by Creech and his associates [1-4] in 1957–58. This method, by which a tumor-bearing area is isolated from the systemic circulation and perfused with high doses of cancerocidal agents through an extracorporeal circuit, permits increased concentrations of chemotherapeutic substances to be delivered to a tumor without an increase in systemic toxicity. Creech and associates [5] have found that some types of tumors, particularly malignant melanomas, show a gratifying response to this technic.

Reported here are experiences in this hospital with the technic of isolation-perfusion, a modality that will, it is anticipated, become a useful addition to the therapeutic armamentarium of this cancer treatment center.

TECHNIC OF PERFUSION

The extracorporeal circuit used for isolation-perfusion is diagramed in figure 1. Two types of oxygenators have been used for this purpose: (1) the Baxter disposable lung (bubble dispersion with helix reservoir, shown in figure 1), and (2) the Abbott Pulmo-Pak disposable oxygenator (bubble dispersion type). Both oxygenators have proved more than adequate for the flow rates used in isolation-perfusion. At these low flows, in areas where the central nervous system is not perfused, it is permissible to prime the system with slightly less than the 3 pints of blood recommended by the manufacturers.

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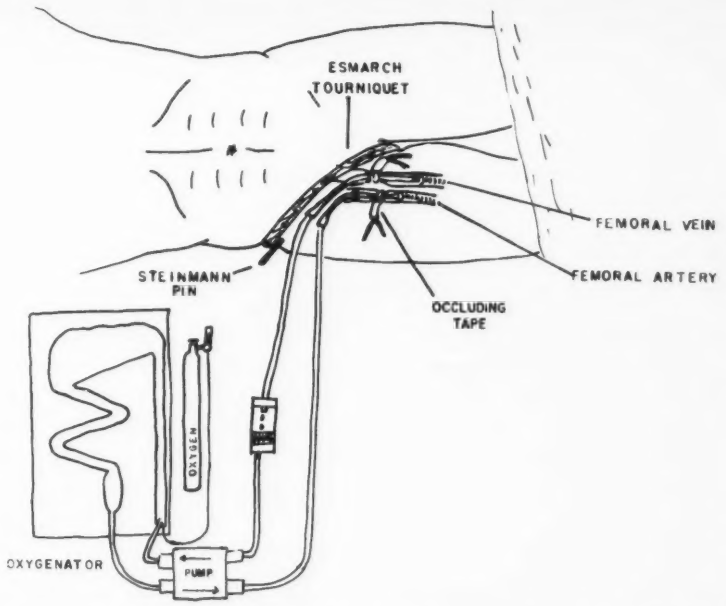

Figure 1. Extracorporeal unit used for isolation-perfusion of an extremity.

The pump used in these cases is a Sigmamotor (finger type) cross-circulation pump; totally occlusive settings are used. A surgical team and a pump team are used in these procedures. While the patient is anesthetized and surgical exposure is accomplished by the surgical team, the pump team assembles the extracorporeal circuit and primes it with fresh blood (both acid-citrate-dextrose solution and heparinized blood have been successfully used) under aseptic technic.

For lesions of the lower extremity, isolation of the extremity is accomplished by means of an Esmarch tourniquet wrapped tightly above a Steinmann pin in the iliac crest (fig. 1). After heparinization of the extremity (or total body heparinization if isolation is expected to be incomplete, resulting in "systemic spillage" into the extracorporeal circuit), the femoral artery and vein are cannulated with plastic disposable catheters.

We believe that it is imperative to use as large a venous cannula as possible, on the basis of laboratory experience in which severe edema resulted from either inadequate venous drainage or excessive perfusion pressure. We have also utilized gravity siphon drainage from the

venous cannula. This places a mild negative pressure on the venous system without the hazard of collapsing the vein about the cannula, thereby creating obstruction to venous outflow. Gravity drainage also avoids the positive venous backwash seen with pumps of Sigmamotor type.

We have found that a perfusion rate of 250 to 300 ml per min is adequate for the usual adult extremity, based upon the absence of ill effects of perfusion, the Van Slyke blood gas studies, and the arterial pH of the perfused blood. The chemotherapeutic agents are added to the arterial limb of the pump as advocated by Creech and co-workers.[1-5] The average duration of perfusion has been from 30 to 60 minutes, depending upon the dosage and combinations of drugs used for chemotherapy. We have been fortunate in that isolation in all cases has been essentially complete, as assessed by the addition of Evans blue (T–1824), radioisotopes, or both to the perfusion blood and their subsequent failure to appear in the systemic circulation during perfusion.

CASE REPORTS

CASE 1. An 18-year-old youth was admitted to this hospital on 8 April 1959, complaining of progressive pain and swelling of 6 weeks' duration in the left knee. During the same period of time he had lost approximately 20 pounds in weight. Physical examination on admission revealed a large hard mass on the anteromedial aspect of the upper end of the left tibia. One observer noted hard rubbery nodes in the left groin. Roentgenograms revealed an osteolytic tumor mass, 4 by 6 cm in size, not involving the cortex, at the upper end of the left tibia, interpreted as osteogenic sarcoma. Roentgenograms of the chest revealed a solitary nodule in each lung, which compared with those in films made 1 month prior to admission had increased in size. Alkaline phosphatase was 20.3 King-Armstrong units. A needle biopsy of the tibial tumor performed on 13 May confirmed the diagnosis of osteogenic sarcoma. On 15 May, palliative radiation therapy was begun. Over a 20-day period, a total of 8,000 r was delivered via 3 portals to the upper left tibia.

Subsequent roentgenograms of the chest, taken during and after radiation therapy, showed continued increase in size and number of the metastatic pulmonary nodules. On 19 August, the patient was presented to the tumor board and it was decided that further palliation might be achieved by isolation-perfusion of the tumor with nitrogen mustard (HN_2). Femoral arteriograms made on the day before perfusion showed poor vascular supply to the tumor area, presumably as a result of previous radiation.

Van Slyke gas studies and arterial pH are reported in table 1. A total of 40 mg HN_2 (0.6 mg/kg) was injected into the arterial limb of the pump in 4 doses, 5 minutes apart. Perfusion was then continued for an additional 20 minutes to allow the HN_2 to become inactive. As a precaution, the blood in the pump and extremity was then drained and replaced with fresh heparinized blood.

Approximately 6 hours after perfusion, the patient became nauseated and vomited. The vomiting was relieved by Compazine (prochlorperazine), but the

Table 1. ***Blood gases and pH studies during perfusion***

Case	*Venous O_2 (vol. %)*	*Venous CO_2 (vol. %)*	*Arterial O_2 (vol. %)*	*Arterial O_2 sat. (%)*	*Arterial CO_2 (vol. %)*	*Arterial pH*
1	16. 97	30. 06	19. 28	100. 7	23. 89	7. 54
2	14. 22	36. 51	16. 91	106. 0	29. 01	7. 42

nausea continued for approximately 36 hours. A minimal amount of edema of the perfused extremity was noted on the first 3 days after surgery. This responded well to elevation and an elastic stocking. No appreciable decrease in blood elements was noted as a result of perfusion (table 2). Evans blue (T–1824) was injected into the circuit 10 minutes before completion of perfusion. The spillage into the systemic circulation, as calculated from a peripheral blood sample, was 3/500 of the total dose.

Further roentgenograms of the left leg failed to show any appreciable change in the size or appearance of the tumor. The lung metastases continued to progress. A small pleural effusion was noted on the second postoperative day. A left thoracentesis was performed on the thirtieth postoperative day because of massive effusion and dyspnea. During the eighth postoperative week, the patient died in a state of respiratory insufficiency secondary to almost total destruction of his lungs by tumor.

Table 2. ***Blood elements before and after perfusion***

Sample	*Hematocrit (ml per 100 ml)*	*Blood elements*		
		Leukocytes	*Neutrophils (%)*	*Platelets*
CASE 1				
Preperfusion	47	15, 100	70	587, 876
Postop. # 1	39	17, 900	76	360, 000
Postop. # 2	42	8, 700	64	300, 510
Postop. # 5	43	11, 000	63	474, 032
Postop. # 7	45	13, 150	62	333, 900
CASE 2				
Hematologic studies not available. No bone marrow depression occurred.				
CASE 3				
Preperfusion	40	20, 250	78	407, 040
Postop. # 3	48	7, 150	57	373, 920
Postop. # 5	38	13, 500	78	257, 280
Postop. # 10	42	9, 600	69	218, 520
CASE 4				
Preperfusion	39	6, 300	67	–
Postop. # 6	35	6, 100	73	–

CASE 2. A 25-year-old man was transferred to this hospital from Tripler Army Hospital with an undifferentiated carcinoma metastatic to the right inguinal region, which subsequently proved to be amelanotic melanoma, although the primary site was never established. Symptoms at the time of admission consisted of pain of moderate severity in the right groin and right popliteal region. Physical examination on admission was negative except for a rather large mass in the right groin, a right popliteal mass, a 1-cm lesion in the right axilla, and a palpable right epitrochlear node.

The right axillary mass was removed and proved to be undifferentiated carcinoma, later diagnosed as amelanotic melanoma. Radiation therapy to the right groin and popliteal region was begun. The patient received 1,422 r to a depth of 5 cm to the popliteal mass and 1,300 r to a depth of 6 cm to the inguinal mass over a 13-day period. During this treatment, the lesions of the right leg became larger and were more painful. At that time it was discovered that the patient had a metastatic lesion in the left lung.

Isolation-perfusion of the right leg for purposes of palliation was accomplished on 24 November 1959. The perfusion was regional rather than isolated in order to include the circulation to the inguinal mass. Phenylalanine mustard, 1.2 mg per kg, was given in 4 doses into the arterial limb of the pump.

Postoperatively, the patient had complete relief of the pain in the right leg. On the fifth postoperative day, the tumor mass in the right groin had decreased to approximately one-half its original size, but at the end of the week the mass began to grow again. Pain, however, did not recur at this time.

Five weeks after perfusion, the patient developed a convulsive seizure, for which he was admitted to another hospital. At that time he had generalized adenopathy, hepatic enlargement, and icterus. There were generalized nodular lesions over the skin of the chest, abdomen, arms, and neck. At this time he required narcotics for pain in his right leg. The patient pursued a rapid downhill course and died, presumably of his malignancy, on 13 January 1960. Results of studies during perfusion are shown in tables 1 and 2.

CASE 3. A 12-year-old white boy was admitted to the orthopedic service on 16 November 1959 with a 2-month history of weakness of the right knee. He had experienced a dull ache in the right knee for 1 week prior to admission, and for 3 days had noted swelling in the knee. Physical examination was negative except for a hard swelling of the medial and lateral aspects of the distal portion of the right femur. Initial roentgenograms showed a lesion in this area, with sunburst effect typical of osteogenic sarcoma. Roentgenograms of the chest made at that time revealed a 14-mm density, thought to represent a metastasis, in the right lung. Open biopsy 4 days after admission confirmed the diagnosis of osteogenic sarcoma. After sufficient time for healing of the biopsy wound, perfusion was attempted with a combination of actinomycin D (50 gamma per kg) and radiophosphorus (P^{32}, 2 millicuries). External localization studies made postoperatively with a radiation counter revealed a tumor-thigh concentration of 3:1, but a tumor-epiphysis ratio of only 1.3:1. Hemopoetic studies are recorded in table 2. Postoperatively, this patient had subjective relief of the preperfusion pain, but only for 2 or 3 weeks. Three weeks postoperatively, a new metastasis was seen in the base of the right lung. Five weeks postoperatively, numerous metastatic lesions were noted in the roentgenogram of the chest, with progressive increase of the previously described lesions, and the patient was again requiring narcotics for the relief of leg pain.

CASE 4. This 24-year-old white man was admitted to the orthopedic service of this hospital with a 1-month history of gradually increasing pain in the left knee when squatting. He was referred to this hospital after roentgenograms revealed a sclerotic growth of the distal portion of the left femur. A biopsy on 14 December 1959 confirmed the diagnosis of osteogenic sarcoma. On 22 December isolation-perfusion of the extremity was performed utilizing 4.5 mg actinomycin D and 4 millicuries P^{32}. His postoperative course was complicated by the development of an infection of the cutdown site for the femoral cannulation. The roentgenogram of the chest, clear of metastatic lesions at the time of perfusion, remained normal. It was planned to proceed with radiation of the lesion and if no metastases had developed at that time to amputate the leg. It is interesting to note that this patient had gradual and progressive diminution of symptoms in the affected leg. Five weeks after biopsy, a small sinus tract formed at the biopsy site and continued to drain purulent material and bits of suture material. Postperfusion roentgenograms of the leg revealed an increase in the size of the tumor mass; biopsy was not repeated. Two months after perfusion, roentgenograms of the chest were negative and hip disarticulation was performed. The gross specimen showed growing tumor.

DISCUSSION

The isolation-perfusion in all cases was performed with technical ease. No serious case of bone marrow depression or tissue slough has occurred in this series of patients. The complete isolation of the extremity from the systemic circulation was readily achieved, and is borne out by the dye and radioisotope studies previously outlined and by the absence of postoperative hemopoetic depression in all patients.

The studies of arterial and venous blood gases and pH indicate that the tissue was supplied with an adequate blood flow at the relatively low flow rates of 250 to 350 ml per minute. We have not monitored either arterial blood pressure or temperature in the perfused extremities. We have taken care to ensure that the perfusion blood is warm to the touch, inasmuch as chilling of the extremity could result in a state of vasospasm during the perfusion. We believe also that the incorporation of an oxygenator in the circuit is necessary to avoid hypoxia of the tissues and consequent vasospasm. Vasospasm affecting the blood vessels supplying the tumor would cause the tumor to receive less blood containing the chemotherapeutic agent. Although suggested, it has not been demonstrated conclusively that the action of mustards is augmented under the high oxygen tensions developed by the inclusion of an oxygenator.[1,4]

In the experience of others,[2] osteogenic sarcoma has not responded well to presently available cancerocidal drugs. Studies by Karnofsky and co-workers [6] indicate that radiotherapy before treatment with HN_2 causes a decreased response to the latter. These and other

studies [7] suggest that a course of HN_2 followed by radiation may result in an increased response to both agents. How much of the decreased response to HN_2 after prior radiation is due to obliteration of the smaller vascular channels in the proximity of the tumor has not been determined.

It has also been reported that a previous course of actinomycin D causes an increased response to subsequent treatment with ionizing radiation.[8] It was our hope that the combination of actinomycin D and P^{32} would result in an augmented tumoricidal effect of both agents. To date we are somewhat disappointed with the results (cases 3 and 4).

The technical facility of this type of treatment, the gratifying response of some types of neoplasm, and the promise of more effective agents in the future have established a definite place for isolation-perfusion in the palliation and adjunctive therapy of malignancies.

SUMMARY

The technic of isolating a tumor-bearing extremity from the systemic circulation and perfusing it with cancerocidal agents is described, using a bubble oxygenator to preclude tissue hypoxia and vasospasm, and a Sigmamotor pump. In 4 patients with extensive osteogenic sarcoma or malignant melanoma of the leg, palliative isolation-perfusion was performed. The chemotherapeutic agent—nitrogen mustard, phenylalanine mustard, or actinomycin D and radiophosphorus—was added to the arterial limb of the extracorporeal circuit at a rate of 250 to 300 ml per minute. Perfusion was continued for 30 to 60 minutes. Essentially complete isolation was demonstrated by adding Evans blue or a radioisotope to the perfusion blood. Adequate blood flow was achieved, as manifested by studies of blood gases and arterial pH. No serious bone marrow depression or tissue slough was observed.

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QUALITY vs. QUANTITY OF MEDICAL CARE

Our patients have been told what constitutes good medical care and how much more of it is needed now than in the past. The public is demanding more and more medical care per individual. And while this is good for all concerned, there may come a point at which quality medical care gives way to quantity medical care. This I don't want to see. I believe American medicine should get on with more medical training and soon. If the schools we now have are filled to their capacity, then we must have more schools, or some new and untried methods of training must be attempted. I know there are many physical and financial problems involved in organizing a good school of medicine, and in obtaining candidates for it. I cannot believe that the ingenuity and resources of this nation have reached the point where such an undertaking is impossible. It is medicine's duty to see that this is done.—HARRY C. BATES, JR.: Some Problems We Face. *Virginia Medical Monthly*, December 1958.

Intestinal Protozoa in Family Groups of Four Japanese Villages

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FOR BOTH EPIDEMIC AND ENDEMIC AMEBIASIS, the relative importance of the various modes of transmission is still conjectural. In the few epidemics studied, water has been implicated as the mode of transmission more often than all other known means combined. However, information from such studies may not be applicable to endemic conditions, which are more difficult to judge because several means of exposure may occur simultaneously and each may vary in importance in different parts of the world or even in communities of the same area.

Familial amebiasis has been noted repeatedly and assumed to stem from intrafamilial transmission, with food handlers and direct contacts with infected persons and fomites as corollary means of exposure. Endemic transmission by water, an epidemiologic influence common to all members of a household, has received limited support. Living habits and environmental conditions have been categorized, predicting a correlation between fecal contamination and occurrence of protozoan infections.[1,2]

The present work is concerned with the correlation of protozoan infections with known environmental conditions and family relations in a series of family groups selected from a rural area of Yamanashi Prefecture, Honshu, Japan. The living habits of these people and their agricultural use of night soil distinguish them from populations so studied in other parts of the world.

MATERIAL AND METHODS

Four farming communities in the Kofu valley coooperated in the project. The primary valley comprises about 100 square miles, linked

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with numerous secondary valleys of the enclosing mountains where 2 of the villages are located. Five stools over a 10-day period were requested from each of 1,037 persons from 172 families, an average of 4.94 per person being submitted. The stools were collected at home and examined in a nearby laboratory, using the formalin-ether concentration procedure.[3,4] A family sheet was prepared for basic information: family and individual number, age, sex, family relationship, status of food handler (primary or secondary), and results of the examination.

Sources of drinking water for the 4 villages differed considerably. The village of Mutsusawa, located on a secondary valley where well digging was not possible, obtained water from an irrigation canal, which also served for washing night-soil buckets, clothes, and vegetables. The village Tatomi, on the flat of the main valley, obtained water from ground-level troughs filled from pipes driven into the ground (continuous flow). In the village of Hikawa, wells were in use, some open, some sealed (with pumps). The village Kissawa, located in a secondary valley, used wells, but the steep terrain increased the hazard of runoff water entering them.

No significant variations in toilet facilities, means of sewage and garbage disposal, or household sanitation were observed among villages.

RESULTS

Parasitic Incidence

Helminthic infections were high, the over-all incidence for the more common ones being Ascaris 80 percent, Trichuris 91 percent, hookworm 65 percent, Trichostrongylus species 27 percent, and *Schistosoma japonicum* 33 percent. One or more parasites were found in 96.8 percent of the persons examined; 96.6 percent had 1 or more helminthic infections. One or more protozoa were harbored by 63.5 percent of the population. The incidence of *Entamoeba histolytica* was 21 percent; for other protozoa, *Entamoeba coli* 50 percent, *Endolimax nana* 35 percent, *Iodamoeba bütschlii* 6 percent, *Giardia lamblia* 13 percent (table 1). For the villages Mutsusawa, Tatomi, Hikawa, and Kissawa, the occurrence of *E. histolytica* was 29, 14, 17, and 23 percent, respectively. *E. coli* ranged from 43 to 56 percent, and *E. nana* from 33 to 39 percent.

The family incidence (table 2) of *E. histolytica* (1 or more infections per family) was 69 percent collectively, and for the 4 villages: 84, 54, 75, and 61 percent. Over 90 percent of the families in each village had at least 1 infection of *E. coli*, the over-all figure being 95 percent;

correspondingly for *E. nana*, 85 to 93 percent, and 88 percent collectively. Only 2 of the 172 families were completely free of intestinal protozoa, and 6 had only 1 infection each.

Role of the Mother

Because the mother of the household is commonly the primary food handler and because she is intimate with each family member, an attempt was made to determine whether there was a linkage of familial infections with infected mothers. A correlation was made between protozoan rates in families where the mother was positive, and for comparison, where the father was positive (table 3). For further comparison, a member of the household was selected at random and these members, when positive, were correlated with incidence within their families. The rates for positive mothers, fathers, and chance selectees were, respectively, for *E. histolytica*, 36, 35, and 38 percent; for *E. coli*, 59, 61, and 65 percent; and for *E. nana*, 45, 49, and 49 percent. Differences involved were minimal and without statistical significance.

Table 1. ***Percent of 1,037 persons infected with protozoa in 4 rural Japanese villages***

Parasite	*Mutsusawa (308)**	*Tatomi (229)**	*Hikawa (251)**	*Kissawa (249)**	*Average*
E. histolytica	29	14	17	23	21
E. coli	49	43	52	56	50
E. nana	33	34	39	35	35
I. bütschlii	10	1	6	6	6
G. lamblia	17	11	6	16	13

*Number of persons in sample.

Table 2. ***Percent of families infected* with protozoa in 4 Japanese villages***

Parasite	*Mutsusawa*	*Tatomi*	*Hikawa*	*Kissawa*	*Average*
E. histolytica	84	54	75	61	69
E. coli	98	90	100	94	95
E. nana	89	85	93	85	88
I. bütschlii	42	7	33	24	27
G. lamblia	67	42	28	54	48

*One or more parasitic species in at least 1 member of a family.

Table 3. ***Occurrence of specific protozoa in family groups with infected mother, father, or member selected by chance***

Occurrence	*Mother*	*Father*	*Chance selectee*	*Total*
E. histolytica				
Number of families	64	42	32	138
Total members	398	268	209	875
Number infected	145	94	80	319
Percent infected	36. 4	35. 1	38. 3	36. 4
Chi-square	0. 001	0. 221	0. 298	0. 519*
E. coli				
Number of families	113	85	81	279
Total members	678	540	509	1727
Number infected	403	330	331	1064
Percent infected	59. 4	61. 1	65. 0	61. 7
Chi-square	1. 349	0. 057	2. 518	3. 924*
E. nana				
Number of families	94	62	58	214
Total members	574	391	352	1317
Number infected	259	190	172	621
Percent infected	45. 1	48. 6	48. 9	47. 2
Chi-square	0. 951	0. 325	0. 413	1. 689*

*For 2 degrees of freedom
P=0.05 when chi-square=5.991
P=0.01 when chi-square=9.210

Another correlation with even better defined categories was made as a further test of the possible role of the mother in intrafamilial transmission. Families were selected in which the mother was the *only* adult infected with *E. histolytica*, all members of her own and her parents' generation being negative. Of the 129 children in 34 such families, 23 (19%) were found to harbor this parasite. Similarly, of the 80 children of families where the father was the *only* adult member infected with this parasite, 12 (15%) harbored *E. histolytica*. The differences are without statistical significance. Of the 204 children in the 58 families with no adult member infected with *E. histolytica*, 21 (10%) harbored this parasite.

Seasonal Variations

In order to compare intestinal protozoa in summer and winter, persons in Hikawa and Kissawa were examined 5 times in both January and early September. For the former village, the incidence of *E. histolytica* was 17 and 21 percent in January and September, respectively,

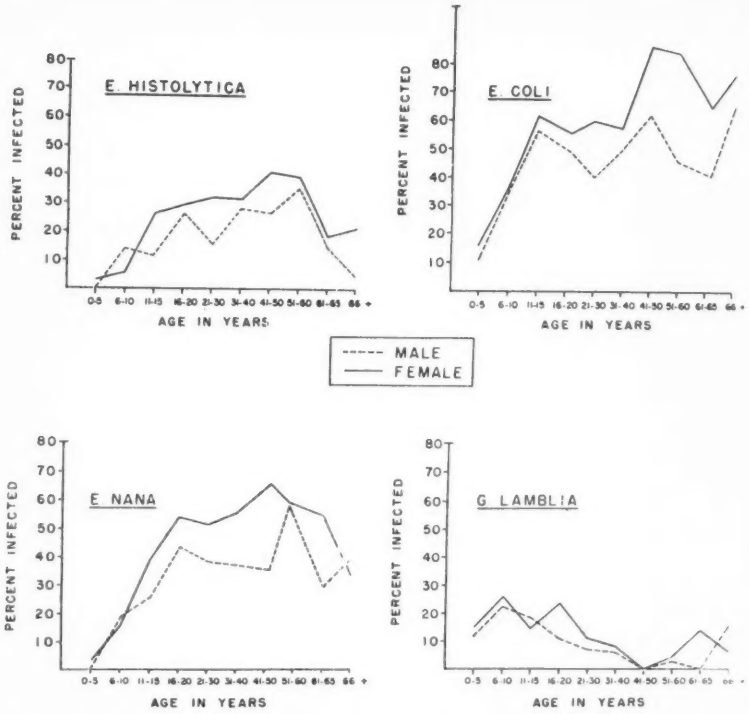

Figure 1. Incidence of protozoal infection in 4 Japanese villages, based on 5 stool examinations in 1,037 persons from 172 families.

while in Kissawa the corresponding figures were 23 and 19 percent. For other protozoa, corresponding differences were limited to 3 percent or less.

Age and Sex

Among the 1,037 subjects, females were in predominance for the 4 protozoan infections (fig. 1). *E. histolytica* and *E. nana* first occurred at near-maximum levels between 16 and 20 years of age and *E. coli* between 11 and 15 years. All infections showed a slight increase throughout adulthood except that a decline occurred at over 60 years of age, particularly with *E. histolytica*. To validate these observations on *E. histolytica* further, data from the present study were combined

with those previously obtained from 1,831 persons in 18 other villages of this same valley area.[5] The greatest difference in sex incidence, in favor of females, occurred in the 16- to 20- and 41- to 50-year groups with P values of .001 and .007, respectively, the difference being statistically significant. Disregarding age, females had a significantly greater over-all incidence than males ($P=.0006$).

Size of Family

Data from the present study were correlated to reveal whether overcrowding in the homes, as reflected by size of family, could account for increased transmission through direct contact. For families of 2 to 5, 6 to 7, and 8 to 10 members, the incidence of *E. histolytica* was found to be 20, 20, and 25 percent, respectively. Likewise, for *E. coli* the incidences were 48, 49, and 53 percent. A trend of higher incidence for larger families may be noted (table 4), but credence is hardly warranted because differences are minimal.

Table 4. ***Correlation of family size and occurrence of protozoal infections in 4 rural Japanese villages***

Occurrence	*Family size (number of members)*					
	2–5		*6–7*		*8–10*	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Number of families	56		78		38	
Total persons	253		506		324	
Infection:						
E. histolytica	50	20	102	20	82	25
E. coli	122	48	249	49	173	53
E. nana	86	34	184	36	115	36
I. bütschlii	14	6	24	5	22	7
G. lamblia	30	12	63	13	43	13

School Attendance

Data correlations were made after the manner of Mackie and associates [6] to determine whether positive school children (7 through 10 years of age) constituted effective leads to the familial occurrence of the major protozoa (table 5). For the collective families of positive and negative children, the respective infection rates were: *E. histo-*

Table 5. ***Infected school child (7 to 10 years of age) as a lead to familial occurrence of protozoal infections***

Parasite	*Child infected*			*Child not infected*		
	*Family members**	*Infections*		*Family members**	*Infections*	
		Number	*Percent*		*Number*	*Percent*
E. histolytica	61	27	44	478	109	23
E. coli	262	153	58	277	123	44
E. nana	127	68	54	412	135	33

*Exclusive of child serving as proband.

lytica, 44 and 23 percent; *E. coli*, 58 and 44 percent; and *E. nana*, 54 and 33 percent. Of 136 cases of *E. histolytica*, only 27 (20%) were identified with children so infected. This is quite in contrast to the findings of Mackie and associates.

DISCUSSION

The high frequencies of intestinal protozoa reported for Yamanashi Prefecture are not representative, since the several villages were selected because of known high rates of infection. Wykoff and coworkers [5] found that the incidence of *E. histolytica* were as low as 0 to 10 percent for a group of villages on the flat of the main valley, whereas much higher rates occurred in the narrow secondary valleys. The family incidence (1 or more infections per family) in the current study revealed that the threat of exposure was imposed on essentially all families, since only 2 of 172 families were found to be completely free of protozoa and only 6 had as few as 1 member infected.

In spite of the fact that the mother is generally the primary food handler and the one most intimately associated with all members of the family, protozoan incidence was about the same for family groups whether the mother, father, or a family member selected at random served as the positive proband. This correlation, then, failed to give support to food handling and direct personal contacts as primary factors of transmission.

The fact that *E. histolytica* and other intestinal protozoa occurred more frequently in females than in males is in agreement with the postulation of Eyles and associates [1] that of the several modes of transmission, direct contact with infected persons and contaminated

articles is in best accord with this sex incidence. A critical point of interpretation might be imposed, namely, that only the *differences* in incidence between males and females are thus accounted for and that still other means of transmission might well contribute to the over-all incidence common to both sexes.

Considerable variation in the age-incidence pattern for intestinal protozoa of different populations has been reported.[7-9] A well-defined increase in incidence during childhood occurs consistently, but the rate of acquisition and the earliest age at which a near-maximum incidence prevails vary greatly. The incidence during adult life may either decline, remain at a constant level, or increase slightly. Eyles, Jones and Smith [1] postulated that maximum acquisition during childhood, followed by a decline in adulthood (as in their population) could again be best explained by direct contacts. An alternative conjecture appears indicated, namely, that the earliest age at which near-maximum levels prevail may be merely a corollary of over-all prevalence or the exposure hazard it reflects—rapid acquisition being associated with high incidence and a retarded acquisition with low incidence. When sanitation is poor, rapid acquisition and a near-maximum incidence within 5 to 10 years could be expected, with minimal increase thereafter. Conversely, good sanitation would minimize contraction rates, with maximum levels delayed until young adulthood, followed by a decline due to spontaneous loss of infection exceeding new infections, as assumed by Eyles and co-workers; more recently, Beaver and associates [10] experimentally demonstrated spontaneous losses of *E. histolytica*.

In the past, food handlers and direct contacts with infected persons and fomites have been considered the means of intrafamilial transmission. It appears that water can also account for such linkage. Contaminated private water supplies or sections of public water systems might account for "familial linkage" when several members of a household seek medical advice. If the Mantetsu water-borne outbreak of amebiasis in Japan [11] had been overlooked, as it could easily have been, family groups infected there would—upon their return to communities in the United States—have constituted classic examples of "familial linkage" of protozoan infections.

Eyles and co-workers [1] reported a direct correlation between size of family and occurrence of intestinal protozoa, and suggested that this could be best explained on the basis of transmission by direct contact. However, a bias in their correlations was noted by Brooke and associates [12] and revised figures were not supportive. A trend toward higher incidence for larger families was evident in Japanese

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families, but differences were minimal and credence is hardly warranted. In any case, transmission by direct contact would merely explain the *differences* of incidence, not the total occurrence of infections.

Since exposure to intestinal protozoa is categorically linked with fecal wastes, attempts by Eyles, Jones and Smith [1] and by Mackie and associates [2] to distinguish categories of sanitation are noteworthy. Attempts to do so for our population were made, and judged futile. It was apparent that all rural Japan is far below the poorest groups of these other investigators, most of whose people belonged to the better categories, so that according to their thesis, most of rural Japan should have high rates of infection. This is not the case.[5, 13]

Briefly, the epidemiologic complex in this study embraced certain factors that seemed to be uniform throughout rural Japan. The low level of sanitation correlated with potentials for transmission by food handlers and direct contacts with infected persons and fomites; flies were abundant, with toilets and night-soil storage tanks available as breeding sites; practices of using night soil were generally the same in all areas; and habits of living were standardized by tradition. Nonetheless, the only factor as variable as the wide range of protozoan incidence among the rural communities seemed to be the domestic water supply. The 4 villages studied represented a transition from hill to valley terrain, with a corresponding decline in incidence of protozoa and reduced threat of water contamination.[5]

It seems likely that the combined influences of food handling and of contacts with infected persons and contaminated objects did not constitute the primary means of transmission of protozoa in the population studied. Furthermore, variations in the relative importance of the several modes of transmission may coincide with levels of incidence; for example, when the incidence is high, water is apt to be the dominant means of transmission, whereas other factors may be relatively more important under moderate or low endemicity.

SUMMARY

The endemicity of intestinal protozoa was studied in 172 family groups of 4 rural villages of the Kofu valley, Japan. Only 2 of these families were completely free of protozoa, the incidence by family for *Entamoeba histolytica*, *Entamoeba coli*, and *Endolimax nana* being 69, 95, and 88 percent, respectively. Among 1,073 persons from the 172 families, the corresponding frequencies were 21, 50, and 35 percent. Among the 4 villages, the highest rate in individuals was 29 percent.

No seasonal influence was noted. Females had significantly higher rates of infection, and near-maximum incidence for *E. histolytica* and *E. nana* occurred in the 16- to 20-year age group. The data did not reveal that infections in a family were particularly associated with 1 member more than another. Size of family and resulting crowding did not appear to be an epidemiologic influence of any consequence.

Community-wide transmission was indicated, overshadowing intrafamilial transmission, to whatever extent it occurred. The epidemiologic picture embraced a series of factors that appeared uniform for rural Japan (sanitation, personal hygiene, prevalence of flies, practices of handling night soil, and general living habits) and that could not account for the variation of protozoa from one village to another. The water supply, however, was a variable related to incidence. It is proposed that where incidence is high, as in the present study, water may be the predominant means of transmission, whereas other factors may be relatively more important in areas of moderate or low endemicity.

ACKNOWLEDGMENT: The authors are indebted to Col. R. L. Hullinghorst, Dr. S. Mitsui, Yamanashi Department of Public Health; Dr. Y. Komiya, National Institute of Health, Tokyo; Dr. S. Sugiyura, Yamanashi Medical Research Institute; and Dr. M. Yokogawa, Institute of Public Health, Toyko, for their professional support. For technical services they wish to thank H. Kutsumi of National Institute of Health, S. Asakura, Y. Hishinuma, R. R. Williams, and T. J. Styles.

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CORRECTION

In the article by Richard D. Levere and Eddy D. Palmer, "Simple Tubeless Gastric Analysis by the Desmoid Pill Technic," which appeared in the July 1960 issue of the *Journal*, the first complete paragraph on page 784 should read as follows:

"It is important that any medications that act as reducing agents be discontinued during the test period. If not, the urine specimens must be heated with acetic acid, because methylene blue has a blue color only in its oxidized form. For obvious reasons, antacids and antispasmodics should also be discontinued during the test period."

Penicillin-Resistant Gonorrheal Urethritis in Male Personnel

LIEUTENANT RICHARD K. MEAD, MC, USNR
LIEUTENANT NORMAN F. MOON, MC, USNR
CAPTAIN LAWRENCE L. BEAN, MC, USN

IT HAS BEEN SUGGESTED in previous medical reports[1-4] that gonorrheal urethritis may be clinically resistant to penicillin. Other investigators[5,6] have stated that an infection persisting after penicillin therapy is actually a reinfection or an inadequately treated initial infection. Lodin,[5] in Sweden, doubted the existence of resistant strains; he claimed a cure rate of 100 percent if due account were taken of reinfections during treatment.

In the summer of 1958 it became apparent to physicians of this station hospital that the treatment of gonorrhea was becoming complicated by the appearance of strains clinically resistant to penicillin. This report presents observations on 11 such cases seen during a 6-month period.

METHODS

Military personnel with possible venereal infections are first seen at military sick call. A routine smear and culture of the urethral discharge or lesion and bacterial sensitivity tests are performed. Cultures are plated on chocolate agar and grown in an atmosphere of 10 percent carbon dioxide. Sensitivity testing is performed using disks, each containing 2 units of penicillin.

Men with venereal disease are sent to the sanitation section for contact reporting. This section follows the treatment of military cases until the man is considered cured by the medical officer.

If the original urethral smear demonstrates gram-negative intracellular diplococci, the patient is considered infected with *Neisseria gonorrhoeae*, and he is treated as such. The patient is placed under

From Station Hospital, Navy No. 3912, FPO San Francisco, Calif. Captain Bean is now assigned to Marine Corps Base, Camp Pendleton, Calif.

medical observation and not allowed liberty for a minimum of 14 days. This medical restriction is maintained in all cases until cure is achieved, thus preventing transmission of infections and possible reinfections. For the first 4 days, the patient receives a daily dose of 600,000 units of procaine penicillin G intramuscularly. If a discharge is still present on the seventh day, when the patient is again seen, treatment is continued or modified as needed.

When the problem of clinical resistance became apparent, a spot check was performed on the potency of penicillin used. The listed dosage corresponded satisfactorily with actual potency.

CASE MATERIAL

The records of the bacteriology department were carefully checked, and the name of each person whose urethral smear was positive for gonococci was entered in the worksheet. Any name appearing twice within a period of 40 days was checked against the clinical records of the military sick call and the sanitation section. Where possible, these persons were personally interviewed by one of us. All patients were male military personnel. To be included in the reported series,

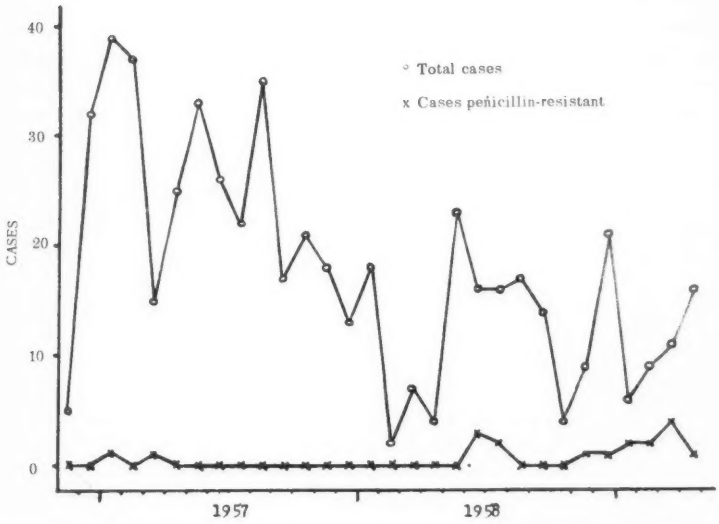

Figure 1. Incidence of penicillin-resistant cases (November 1956-April 1959).

Table 1. ***Chemotherapy dosage schedule in 11 cases of penicillin-resistant gonorrheal urethritis***

Case	*Procaine penicillin G (units daily)*	*Intermediate agent and daily dosage**	*Curative agent and daily dosage*
1	600,000 x 4	none	oxytetracycline 2 gm x 10
2	600,000 x 4	none	chloramphenicol 1 gm x 7
3	600,000 x 4	none	chloramphenicol 1 gm x 7
4	600,000 x 6	sulfadiazine 4 gm x 6	chloramphenicol 1 gm x 6
5	600,000 x 5	none	oxytetracycline 1 gm x 10
6	600,000 x 5	sulfisoxazole 4 gm x 10	chloramphenicol 1 gm x 7
7	1.2 mil x 4	sulfisoxazole 4 gm x 10	chloramphenicol 1 gm x 7
8	600,000 x 5	sulfisoxazole 4 gm x 7	erythromycin 2 gm x 5
9	600,000 x 5	oxytetracycline 1 gm x 10 erythromycin 1 gm x 14	sulfadiazine 4 gm x 13
10	600,000 x 4	sulfisoxazole 4 gm x 10	chloramphenicol 1 gm x 7
11	600,000 x 4	none	chloramphenicol 1 gm x 10

*Urethral smears remained positive for gonococci after the indicated course with these agents.

the case had to meet certain rigid requirements: 1. Repeat positive urethral smears had occurred within 30 days of the original laboratory diagnosis. (In actuality, the longest interval between positive smears was 20 days.) 2. The patient had been under medical restriction during the interval between positive smears, with no chance for reinfection. 3. The patient had received at least 4 daily injections, each of 600,000 units of procaine penicillin G, following the initial positive smear. 4. The patient had no evidence of complications. Patients meeting these requirements were considered to have gonorrheal urethritis clinically resistant to penicillin.

RESULTS

Incidence

In order to ascertain whether the phenomenon was new to this area, or had been previously present and unrecognized, the study was carried back through November 1956. It was found that although 2 sporadic cases occurred in early 1957, the problem did not become significant until the summer of 1958 (fig. 1). The present study comprises only the period November 1958 through April 1959 because complete records are not available in each case for previous periods. During this 6-month period, 11 cases of gonorrhea clinically resistant to

penicillin were seen (table 1). These comprised 15.3 percent of all gonorrheal cases seen during that period.

In Vitro Studies

Bacterial cultures and disk sensitivities (table 2) were performed in all but 1 of the cases. (This patient, case 11, was seen in consul-

Table 2. ***Bacterial sensitivity studies* in gonorrheal urethritis clinically resistant and clinically sensitive to penicillin***

Case	*Pen*	*Cht*	*Chm*	*Dih*	*Oxy*	*Tet*
CLINICALLY RESISTANT						
1	RR	RR	s	s	RR	
2	s	RR	s	RR	RR	
3	RR	s	s	RR	RR	s
4	RR	s	s	RR	RR	s
5	RR	s	RR	s	s	
6	s	s	s	RR	s	s
7	s	s	s	RR	s	s
8	RR	s	s	RR	s	s
9	RR	s	s	RR	RR	s
10	s	RR	RR	RR	s	s
11	not tested					
CLINICALLY SENSITIVE						
1	s	s	s	s	s	
2	s	RR	s	s	s	s
3	s	s	s	RR	s	s
4	s	RR	s	RR	s	s
5	s	s	s	RR	RR	s
6	s	s	s	RR	RR	s
7	s	s	s	s	s	s
8	s	RR	s	RR	RR	RR
9	s	RR	s	RR	RR	RR
10	s	s	s	RR	s	s
11	s	RR	s	RR	RR	s
12	s	s	s	RR	s	s
13	s	s	s	RR	s	s
14	s	s	s	RR	s	s

*B-B-L Sensi-discs were used for all studies:
Pen — penicillin, 2 units
Cht — chlortetracycline, 5 mcg
Chm — chloramphenicol, 5 mcg
Dih — dihydrostreptomycin, 10 mcg
Oxy — oxytetracycline, 5 mcg
Tet — tetracycline, 5 mcg

tation by this hospital but did not receive treatment here.) For purposes of comparison, sensitivity studies are also reported for 14 consecutive cases of gonorrhea, in patients seen during the same period who were clinically cured by penicillin in the previously mentioned dosages. It can be seen that in vitro studies and in vivo responses did not correspond in every case, as organisms from 4 (36%) of the study group were sensitive in vitro but resistant in vivo. It is unfortunate that dilutional studies were not available at this institution, as the disk method of determining sensitivity is considered slightly less reliable.[7] Some investigators,[8,9] however, believe that disk sensitivities are perhaps better than serial dilutions in routine tests because of the many variables in the latter method. Because of the fastidious nature of the organism, the specimens could not be sent to a facility offering this procedure. It is of note that in all patients with gonorrhea who responded to penicillin and on whom sensitivity studies were run, the organisms were sensitive in vitro as well as in vivo. A second point of interest is that in 2 patients (case 1 and 10) the organism showed resistance in vitro to the agent used to bring about eventual cure.

DISCUSSION

As early as 1943 reports on the efficacy of penicillin in treating gonorrhea were appearing in the literature. Although in 1945 Miller and Bohnhoff[10] reported the development of in vitro resistance to the drug, this did not apparently become clinically significant until very recently. In 1957, Reyn, Korner and Bentzon[11] reported that they had not been able to isolate, from patients, strains highly resistant to penicillin.

Lodin[5] states that gonorrhea should be treated with relatively low doses of penicillin, that patients are being overtreated, and that most continuing gonorrheal discharges are probably reinfections. Brown and Garson[6] believe that the treatment of choice for uncomplicated gonorrhea is a single intramuscular injection of 600,000 units of procaine penicillin G in oil with 2 percent aluminum monostearate (PAM) or benzathine penicillin G. Other clinicians[1-4,12] also advocate a single injection of 600,000 units. Kirby[13] states that treatment failures are not due to the development of penicillin-resistant gonococci and that few if any cases fail to respond to a second course of daily injections of 600,000 units over a 2- to 4-day period.

In a recent article, Fiumara and co-workers[12] state that there has not been a clinical case of penicillin-resistant gonorrhea in the records of the Massachusetts Public Health Service. Spot checking with

cultures during the 5 years up to 1958 showed all cultures to be sensitive to penicillin. Their treatment for acute gonorrhea in the male patient was 600,000 units of procaine penicillin in aqueous suspension as a single dose. They had a cure rate of 95 to 98 percent; the 2 to 5 percent who failed to respond in 48 hours to the initial injection were given an additional 600,000 units. Those who were apparent failures admitted re-exposure.

The minimum total dose used at this hospital is 2,400,000 units of procaine penicillin over a 4-day period. Occasionally a patient is given a trial of additional doses if the infection appears to be abating. One patient received 6 daily doses. These doses would appear more than adequate when compared to the optimum dosages quoted in the literature.

Since all patients in the present study are military personnel, daily injections are no problem. A further advantage in dealing with service personnel is that the men's recreational activities can be restricted, eliminating the possibility of reinfection while under observation. With this in mind, it seems highly improbable that these patients were either reinfected or received inadequate doses of penicillin.

SUMMARY

Bacterial sensitivity studies are presented in 11 cases of gonorrheal urethritis clinically resistant to treatment with a minimum of 4 daily injections of 600,000 units of procaine penicillin G. These cases comprised 15.3 percent of all gonorrhea seen during a 6-month period in male military personnel. In 4 of these cases, the organism exhibited in vitro sensitivity to penicillin by the disk method. In 2 patients the organism was resistant to the antibiotic subsequently used to effect a cure. The controversy concerning the existence of gonorrhea clinically resistant to penicillin is discussed in a brief review of the pertinent literature. In view of the fact that the penicillin regimen in the cases presented was more than adequate by current standards and that the patients had no opportunity for re-exposure, reinfection and inadequate penicillin dosage seem improbable explanations of the failure of penicillin therapy in these cases.

ACKNOWLEDGMENT: The authors wish to thank Dewey Loselle, ChMedSerWrnt, USN, head of the sanitation section at this station hospital, for his assistance and suggestions, and Susumu Kubo, for laboratory assistance; and the 406th General Medical Laboratory, Camp Zama, Japan, for penicillin assay.

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THE INDISPENSABLE DRUDGE

The printed literature of medicine remains the indispensable archive of its scientific, clinical, social and economic progress, as well as of its philosophy; the permanent depository of discovery whether in the physical sciences or in the development of ideas. And in order that the record may be legible, the editor, like Samuel Johnson's lexicographer, a harmless drudge, enjoys also a reflected and anonymous indispensability.—Joseph Garland: Editor Resartus. *The Journal of the Canadian Medical Association*, January 30, 1960.

Field Testing Program in Clinical Psychology

ROBERT J. MARSHALL, PH.D.

BECAUSE THE GOALS AND FUNCTIONS of the Clinical Psychology Field Testing Program can best be understood in context, it is necessary to scan briefly particular developments in military field psychiatry, the mental hygiene program in the Army, the field social work program, and the traditional role of military clinical psychology.

The idea for mental health personnel to work with the soldier in the field originated in World War I, was implemented in the latter half of World War II, and came to fruition during the Korean conflict. "Combat psychiatry," described by Glass [1] and the Department of the Army,[2] emphasized the need to examine and treat the embattled soldier as soon as signs of psychiatric disturbance were manifest and to accomplish this as close to the front lines as practicable. Emphasis was placed on limiting any secondary gain associated with medical recognition of emotional disturbance and on preventing fixation of symptoms and development of the role of the psychiatric patient.

In other military settings, such as basic training centers and military specialty schools, environmental stresses seem to induce or make more manifest a high frequency of psychiatric symptoms. To cope with the psychiatric problems, the Army established the Mental Hygiene Consultation Service (MHCS)[3-5] in larger military centers. The MHCS has begun to perform more social and preventive psychiatric functions, by which, for example, the psychiatrist acting as mental hygiene consultant assists commanding officers and various military agencies in defining and solving the mental hygiene problems of the military community. A secondary yet important MHCS function involves a diagnostic answer to the question: "Does this soldier have

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the psychologic resources to cope with and function in the military environment?" Still another function, which is broadly therapeutic, is that of organizing the resources of the military community so that they may readily be used to help a given trainee mobilize his adaptive potential in mastering the problems of military life.

A number of rules of thumb have proved to be successful in mental hygiene programs: (1) The patient is seen soon after a disturbance is reported. (2) The patient is so treated that self concepts relating to his being a psychiatric "casualty," disabled, or "crazy" do not arise or are dispelled, and he is consistently and firmly encouraged to maintain his identity as a soldier.[6] (3) Conditions are avoided that foster the notion that the patient is in "protective" medical hands as contrasted with "punitive" military control. (4) The patient, if his disturbance warrants, is seen by a person having his peer group characteristics, such as age and rank. (5) The patient is seen in the "field" rather than in the clinic, if possible. (6) All cases are handled expeditiously.

This approach may be contrasted with an orientation that may involve frequent clinic or hospital visits, an atmosphere of "white coats," or even hospitalization in order to accomplish extensive diagnostic and evaluative procedures that may seriously interfere with the continuity of basic training.

These considerations have allowed for the extensive use of field social work specialists (SWS), who function under the close supervision of social work officers (SWO). The typical SWS, at least at this army post, had been drafted after 4 years of college training in social sciences and often had some experience related to social work. The SWS was an important link or mediator between patient, commanding officer, clinic staff, and other military agencies. He also had the responsibility of conducting initial case interviews, and of assuming case-work functions consonant with his competence and always under direction of his SWO supervisor. It may be emphasized that the descriptions of the social work specialist and the clinical psychology specialist have been determined mainly by my own experience at this post. It is quite possible that the quasiprofessional caliber of the specialists may have been atypical relative to other Army settings. On the other hand, it is possible that the attention, instruction, and supervision granted to the specialist raised him to an unusual level of competence.

Before the field aspects of clinical psychology can be introduced, it is necessary to highlight some of the traditional functions of clinical psychology. The triad of diagnosis, treatment, and research is often

advanced as characterizing the work of clinical psychologists in civilian and military settings. Although the emerging role of the Army clinical psychologist includes a relative diminution of the psychodiagnostic function, this function remains a major aspect of the psychologist's contribution. For example, Zehrer states: [7] "In our function as psychologists we devote 40 to 60 percent of our time in a primary justification of our being where we are: in psychodiagnostic aid role."

Granted that the diagnostic function of the psychologist is an important one, and considering the emphasis on the field approach in military mental hygiene activities, it seemed appropriate to search for ways in which clinical psychology could integrate itself into the field program.

EVOLUTION OF CLINICAL PSYCHOLOGY IN FIELD PROGRAM

As already mentioned, the social work section had an important role in the field program. On occasion, the SWO and the SWS needed additional consultation in their joint evaluation of problem patients. The SWO then decided on one or both of 2 alternatives: consult with a psychiatrist, or schedule the patient for psychiatric evaluation. At times a combination of factors favored the evolution of the field program: (1) Psychiatric time was not immediately available except for emergency cases. (2) There was a possibility of referring false positives to a psychiatrist, with consequent loss of valuable psychiatric time. (3) Removing a trainee from his unit and bringing him into a mental hygiene clinic to see a psychiatrist usually supported the trainee's "psychiatric patient role" and complicated the therapeutic strategy.

In some cases it seemed appropriate to take referrals directly from the social work section and examine the trainees psychologically "in the field" to help decide whether the psychiatric referral was advisable. Although the initial purpose was to provide a screening and "protective" service for the psychiatrist, the complementary functioning of psychology and social work in the field soon made other goals and benefits apparent.

GOALS

In July 1957, therefore, the clinical psychology field program was launched in a manner that, except for changing personnel, remained the same until the reporting period of March 1959. The goals of the

program were (1) to provide a finer screening device for psychiatric referrals in order to be more economical with psychiatric time; (2) to offer aid to the social work section in understanding their patients and planning a therapeutic approach; (3) to provide a psychiatrist with a report about a patient before he was seen; (4) to minimize trainees' loss of training time—a goal in particular accord with command requirements for an 8-week training schedule; (5) to diminish the probability that the trainee would develop a self concept detrimental to his functioning as a soldier.

It may be apparent that the above stated goals are similar to the principles of the ongoing military mental hygiene or "psychiatric first aid" approach in general.

PROCEDURE

Actual administration of the field tests involved 2 clinical psychology officers (CPO) and 9 clinical psychology specialists (CPS). The CPO's held a doctorate in clinical psychology. The CPS usually was an enlisted man who had been drafted after completing a bachelor's degree in psychology or social science. The burden of testing fell largely on the shoulders of 3 CPS's—who by no coincidence were the most competent in the section, since only the better technicians were used in the field program. Frequently, the CPO would accompany the CPS to the field to administer or supervise test batteries. One point may be emphasized: the CPS was carefully trained and closely supervised so that his personal integrity and professional competence were well known to the CPO. Without this condition, the field program could not have functioned properly.

The CPS was assigned to a training regiment (as was the SWS) so that he could gain the maximum knowledge of particular field conditions, become acquainted with the men, and also come into closer working relationship with the SWS. Psychologic tests were used selectively, but in accord with sound testing principles and procedures, and oriented toward answering the referral problem or emerging problems. Every effort was made to see the patient immediately. After collecting and scoring the test data, the CPO and CPS reviewed in detail the test protocols. Although the interpretations and write-ups were performed largely by the CPO, the CPS was encouraged to participate according to his ability. Every effort was made to provide at least a verbal report to interested persons the day the patient was seen. Expeditious handling, without sacrificing quality, was primary.

Of the 76 patients included in the program during the 20-month

experimental period, 82 percent were basic trainees, 16 percent were in advanced infantry or specialist training, and the remaining were cadre. The referrals were received from 15 individual sources, mostly from the social work section. Moreover, the fact that more than half the referrals were made by only 4 SWS's reflected a selective influence in referrals. Of these 4 SWS's, 3 represented the most competent of the SWS's, whereas one was the least trained and talented.

In considering the reasons for referral, which were often stated in terms of presenting problems, 6 major categories were noted: (1) poor performance, including anxiety and somatic symptoms; (2) suicidal threats and self-damaging behavior; (3) fears, depression, and anxiety; (4) disobedience and open hostility; (5) intellectual evaluation; (6) personality evaluation; (7) differential diagnosis, such as low intelligence versus schizophrenia. Initially most of the referrals requested "intellectual evaluation." Then, many requests to "evaluate poor performance" were received. A series of requests to evaluate poor performance associated with somatic and psychologic complaints were next received. Subsequent requests were couched in terms of "personality evaluation." One might note that this evolution recapitulates the development of the use of psychologists, beginning with "I.Q. testing" and progressing to a more sophisticated level of "evaluating the person as a whole."

The kinds and numbers of tests administered were determined by the CPO. Considerable emphasis was put on the Rorschach, Draw-A-Person, Wechsler Intelligence Scales, Bender-Gestalt, and Thematic Apperception Test, and on a Military Apperception Test* consisting of 12 pictures portraying various aspects of military life. The absence of such tests as the Minnesota Multiphasic Personality Inventory, Sentence Completion, and tests of concept formation may be noted. Choice of tests was dictated, in part, by the notion that as little time as possible should be spent in contact with the trainee. The consequence of this approach was that approximately 1½ hours was spent with the average patient.

In respect to the conditions under which the patients were tested, one saw a tremendous variation in the place and also in the quality of testing conditions. Places used included Company commander's

*Information may be obtained from the author or from the Clinical Psychology Consultant, Office of the Surgeon General, Department of the Army, Washington, D.C.

rooms, cadre lounges, cadre rooms, empty barracks and day rooms, bivouac, and rifle range. In one instance, a perhaps overly conscientious CPS used his vehicle in which to test a patient during a rainstorm. In general, cadre lounges and day rooms provided an adequate degree of privacy and comfort. A close working relationship with command elements insured better testing conditions and acceptance of the CPS in the field.

RESULTS

The correspondence between psychologic recommendations and social work action was observed in 69 patients (table 1); recommendations were not recorded for the remaining 7 patients. It is noteworthy that the social work section followed the psychologic recommendation in 60 of 69 cases, an agreement of 87 percent. When the psychology section suggested that a patient be referred to a psychiatrist, the advice was followed in 29 out of 30 cases. When the psychologist suggested return to duty in 35 cases, the social work section differed on the side of caution by referring 8 of the 35. In general, then, there was considerable congruence between psychologic recommendation and social work disposition.

Table 1. ***Relationship between psychologic recommendation and social work action in 69 patients***

Psychologic recommendation	*Social work action*		*Total*
	Duty	*Psychiatric evaluation*	
Duty	27	8	35
Psychiatric evaluation	1	29	30
Duty but psychiatric evaluation	–	4	4
Total	28	41	69

Of 41 patients referred to a psychiatrist by the social work section, psychiatric data are available on 36. Comparison of the psychiatric disposition of these patients with the psychologic recommendation (table 2) reveals chance agreement between psychologist and psychiatrist in the 8 cases in which the psychologist suggested duty. However, when the psychologist thought there was sufficient disability to warrant evaluation for hospitalization or discharge, there was more than chance agreement between psychologist and psychiatrist: of 24 patients whom the psychologist recommended for psychiatric evaluation, 17 were discharged or hospitalized.

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Table 2. ***Relationship between psychologic recommendation and psychiatric decision in 36 patients referred to a psychiatrist by social work section***

Psychologic recommendation	*Psychiatric decision*		
	Duty	*Hospitalization or discharge*	*Total*
Duty	4	4	8
Psychiatric evaluation	7	17	24*
Duty but psychiatric evaluation	2	2	4
Total	13	23	36

*No psychiatric data available in 5 of 29 cases.

DISCUSSION

If the goals of the program are related with the outcome, the following conclusions are evident: (1) Of the 27 patients whom the psychologist recommended for duty without psychiatric intervention, none was discharged or came to subsequent psychiatric attention while at the basic training center. If it is assumed that the 27 did not require psychiatric evaluation and that without psychologic advice the 27 would have been referred to the psychiatrist, it follows that considerable psychiatric time and effort had been conserved. (2) It is obviously difficult to evaluate the extent to which the psychologist helped the social work section in understanding the patient and planning effective therapeutic procedures. However, the manner and persistence with which the social work section sought out members of the psychology section as the program developed and also the continuance of the program beyond the reporting period suggest that the psychology program was of real value to the social work section. Subjectively, it was felt that the psychologic information that the SWS received enhanced his security and competence in handling the case. (3) Providing the psychiatrist with a psychologic report before he saw a patient appeared to have the virtue of enabling him to come to a more definitive evaluation of the trainee in a shorter period of time. (4) The relationship between psychology and social work sections unquestionably improved in that their members spent more time together discussing practical and theoretic mental hygiene issues. In general, the esprit of the clinic personnel improved. One reflection of the increased cohesiveness and pride was the development of a professional library and the creation and production of a play, "The Man in the Field," which depicted the clinic's field program

and which was presented to local command elements. (5) Trainees' loss of training time was minimized. The 1½-hour psychologic examination in the field may be contrasted with an estimated 4 hours necessary to travel to, wait for, and engage in a psychiatric interview.

Of course, the advantage of not taking the man from his company area for the evaluation cannot be objectively estimated. Also, it is difficult to assess what effect being tested by a peer in a familiar setting had upon the trainee's self concept. It was consistently reported, however, that patients in the field had a lower anxiety level—manifested by more cooperation and by fewer questions about the meaning of the tests and the trainee's future—which seemed to reflect less conflict in soldier-patient roles.

SUMMARY

The development and philosophy of field psychiatry, the mental hygiene program, and field social work in the Army are briefly scanned. A common denominator appears to be the mobilization of the military community's therapeutic resources so that army personnel can more easily master the problems of military life. There has also been emphasis on reducing secondary gain associated with medical recognition of psychologic distress. One function of the Mental Hygiene Consultation Service (MHCS) is the early and expeditious diagnosis and treatment of the soldier in situ, thus preventing a "patient's role" from crystalizing and utilizing enlisted personnel as important diagnostic and therapeutic adjuncts.

At this army post, clinical psychology, in the traditional role of psycho-diagnostic aid, integrated the above policies into its program. Taking referrals largely from and working closely with field social work specialists and their social work officer supervisors, clinical psychology officers, together with enlisted clinical psychology specialists carefully trained and closely supervised by these officers, tested trainee patients in the field. Major projectives, especially the Rorschach and thematics, were administered in a variety of field settings. Typically, the psychologic evaluation assisted in determining whether psychiatric consultation was advisable and in making the trainee's behavior more understandable to the social work section. Agreement between psychologic recommendation and social work action was high (87%).

The results of the program were: (1) The time of an often overburdened psychiatrist was conserved and more economically utilized.

(2) The competence and sureness of the social work section in handling a case seemed to be enhanced by virtue of the important psychologic information made available. (3) The over-all professional interrelationship of the psychology section and social work section was considerably augmented. (4) In addition to the fact that evaluation by MHCS minimized the trainee's loss of training time and perhaps of subsequent participation in training procedures, it was felt that psychologic testing in the field minimized his conflicts and his anxiety concerning his examination in a mental hygiene clinic.

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DIAGNOSTIC DIFFICULTIES

The omission of a single laboratory determination may cause a metabolic defect to remain undiagnosed in spite of extensive investigation.—Helen Davis: Metabolic Causes of Renal Stones in Children. *Journal of the American Medical Association,* December 19, 1959.

Hemostasis

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CAPTAIN HAROLD S. RAMOS, USAF, MC

THE PAST DECADE HAS WITNESSED many advances in the study of hemostasis. Rapid development, broad scope, and varying locale have characterized discoveries in the field, and in turn have led to much of the confusion in terminology. The numerous names [1] applied to a single coagulation factor have discouraged many a reader from more than a glance at articles devoted to the subject.

Hemostasis can be presented simply and this is the object of our review. But in order to simplify any concept, an understanding of the terms used is necessary. We cannot hope to explain the derivation of the many titles available for the plasma factors of coagulation, for to do so would require a history of the subject. The best approach for the uninitiated is to select a single name for each of the plasma factors and become familiar with it. Table 1 lists the more common synonyms for the coagulation factors.

NORMAL HEMOSTASIS

Hemostasis results from an interaction of blood factors and blood vessels. A derangement of either results in bleeding. Certain phenomena are responsible for the initial but temporary arrest of blood flow. These primary factors of hemostasis are vascular contraction, capillary adhesiveness, and platelet agglutination.

Vascular contraction is responsible for the normal bleeding time in hemophilia. Its value in stopping bleeding was known for centuries, then forgotten, until re-emphasized by Magnus [2] in 1923. After showing that normal arteries contract intensely following injury, Magnus concluded: "The process of hemostasis must be considered more than heretofore a property of the vessel itself." Injury to a

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Table 1. ***Current terms for coagulation factors***

Terms used in discussion	*Definition*	*Synonyms*
Antihemophilic globulin (AHG)	The plasma factor necessary for thromboplastin formation but deficient in classic hemophilia. Antihemophilic globulins (AHG) are plasma proteins, principally $\beta 2$ globulins.	Factor VIII Platelet cofactor 1 Antihemophilic factor A Thromboplastinogen Prothromboplastin A Plasma thromboplastic factor A
Plasma thromboplastin component (PTC)	The plasma factor necessary for thromboplastin formation but absent in Christmas disease.	Factor IX Platelet cofactor 11 Antihemophilic factor B Plasma thromboplastin factor B Prothromboplastin B Autoprothrombin 11 Christmas factor
Plasma thromboplastin antecedent (PTA)	A plasma factor necessary for thromboplastin formation; deficiency results in a hemophilioid syndrome.	Antihemophilic factor C
Hageman factor	A plasma factor deficiency of which results in clotting anomaly in vitro but without clinical hemorrhagic manifestations.	
Factor V	A factor disappearing on heating or storing of oxalated plasma; required for the formation of thromboplastin and for the conversion of prothrombin to thrombin. It is consumed in coagulation.	Labile factor Proaccelerin Ac-globulin
Factor VII	A plasma factor required for the conversion of prothrombin to thrombin. It is stable on storage and not consumed in coagulation.	Stabile factor Proconvertin Serum prothrombin conversion accelerator (SPCA) Cothromboplastin Autoprothrombin 1
Stuart factor	A plasma factor required for the formation of thromboplastin and the conversion of prothrombin to thrombin. It is stable on storage and not consumed in coagulation.	

vessel sufficient to permit an escape of blood produces contraction. Little is known about this reaction, which is probably reflex in nature. It is independent of platelets and administration of neither heparin nor Dicumarol prevents it.[3]

Capillary adhesion develops when intimal endothelial cells are pressed together. The resultant stickiness or adhesiveness may permanently glue the vessel walls together. This phenomenon has a prominent role in lower forms of life. In the toad, the adhesive force generated by the capillaries can withstand a pressure of 200 mm Hg.[4] Capillary adhesion is probably the means whereby bleeding in hemophilia is ultimately arrested.[5]

Platelet agglutination is directly related to these primary phases of

hemostasis. Aside from the debatable point that platelets may be capable of initiating fibrin formation,[6] the platelet clot itself is an important mechanical structure. This is emphasized in congenital afibrinogenemia, where normal platelet function explains the relative mildness of bleeding, despite incoagulability of the shed blood.[7,8] In addition, platelets also release 5-hydroxytryptamine, a vasoconstrictor substance.[9,10] This vasoconstrictor may complement reflex vascular contraction and probably continues the effect when the reflex action ceases.

These primary hemostatic factors maintain hemostasis until coagulation begins and they are active while the process of clot formation develops. The formation of the fibrin clot constitutes the secondary hemostatic barrier and its efficiency depends on the concentration of clotting factors and platelets in plasma.[11,12]

Exposure of blood to a foreign surface activates the clotting process. Platelets disintegrate and thromboplastin, thrombin, and fibrin are formed. Only the latter is visible, and even though the interactions of the plasma factors are rapid, they are not entirely complete at the moment fibrin becomes visible. To present the scheme of coagulation, we have adopted a 3-stage rocket concept (fig. 1). Each stage will be described in detail, with the realization that in physiologic clotting, there is no separation in time and marked overlapping exists between all the stages. Utilizing the rocket concept, the steps in coagulation are presented as stage 1, the formation of thromboplastin; stage 2, the formation of thrombin; and stage 3, the formation of fibrin. The reactions of the coagulation factors in stages 1 and 2 are very complex and not completely understood. Although definite proof of each factor's interrelations is not yet available, so that this scheme may not be completely acceptable to some in the field of coagulation, it has been exceptionally useful in the hematology training program at Walter Reed Army Medical Center.

Stage 1. Formation of Thromboplastin

Thromboplastin is a term, not a specific entity. The word refers to a function, that is, the ability of a preparation to activate prothrombin. "Tissue" thromboplastin is released by injured tissue and may be extracted from tissues such as lung or brain. "Plasma" thromboplastin refers to the inherent prothrombin-converting ability of plasma. This activity is generated by the interactions of various plasma components and platelets.

The plasma components bear significant titles: plasma thromboplastin component (PTC), plasma thromboplastin antecedent

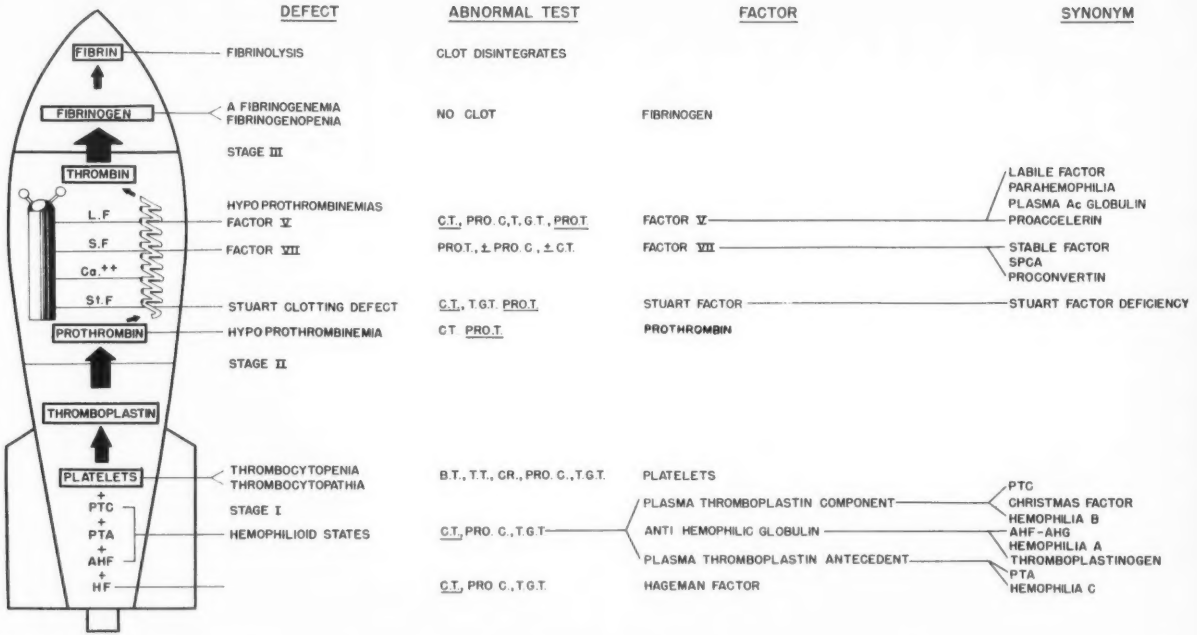

Figure 1. Atlas of coagulation. C.T.=clotting time; Pro. C.=prothrombin consumption; B.T.=bleeding time; Pro. T.=prothrombin time; T.G.T.=thromboplastin generation test.

(PTA), and antihemophilic globulin (AHG). All are present in normal plasma and each is necessary for the generation of thromboplastin. Hageman factor, a more recent discovery, is also present in plasma; and though it is not necessary for the formation of thromboplastin in vivo, it is necessary in vitro. Information on the order of reaction of these factors has been obtained by exposing various combinations of them to a foreign surface. PTC is activated first. It reacts with AHG, PTA, and platelets. The product of this reaction plus factor V (labile factor) plus Stuart factor yields thromboplastin.[13] Factor V normally disappears during clot formation. It is not consumed when there is a deficiency of PTC, PTA, AHG, or platelets. This tends to support the concept that it is required late in the formation of thromboplastin.[14] AHG, which also disappears during clotting, even in thrombocytopenia, does not disappear in PTC deficiency. This suggests that PTC activates AHG before the reaction of AHG with platelets.[15]

The reaction of PTC, calcium, and AHG produces a substance that niitiates clumping of platelets. The latter, in turn, throw out pseudopodia and undergo partial dissolution, a process sometimes referred to as "viscous metamorphosis." As the platelets disintegrate they discharge granules bearing platelet cofactor 3, a material required for normal generation of thromboplastin.[16] The formula for thromboplastin formation therefore is:

$$\text{PTC} + \text{AHG} + \text{platelets} + \text{PTA} + \text{factor V} + \text{Stuart factor} + \text{CA}^{++} \longrightarrow \text{thromboplastin}$$

If we inspect our coagulation rocket at this point (figs. 1 and 2), we observe that thromboplastin is the fuel required to propel the first stage of the rocket. The fuel is generated by the plasma precursors and the platelets. Absence or inhibition of any factor or of the platelets prevents the proper mixing of the first-stage fuel. "Take-off" of the rocket is delayed by the faulty priming mechanism and the first stage leaves the theoretic launching pad slowly. It falters because the fuel, "thromboplastin," is generated poorly. This not only impedes stage 1 of the coagulation rocket, but affects the other stages as well, for thromboplastin not only propels the first stage, but activates the formation of thrombin, the propellant of the second stage. As a result, prothrombin is not used properly and after coagulation an excess remains in the serum. The combined delay in the firing of the first and second stages prolongs the period required for fibrin formation. The result is a delayed clotting time of whole blood.

Any defect of the first-stage plasma factors is therefore characterized by a prolonged clotting time, an abnormal prothrombin consumption

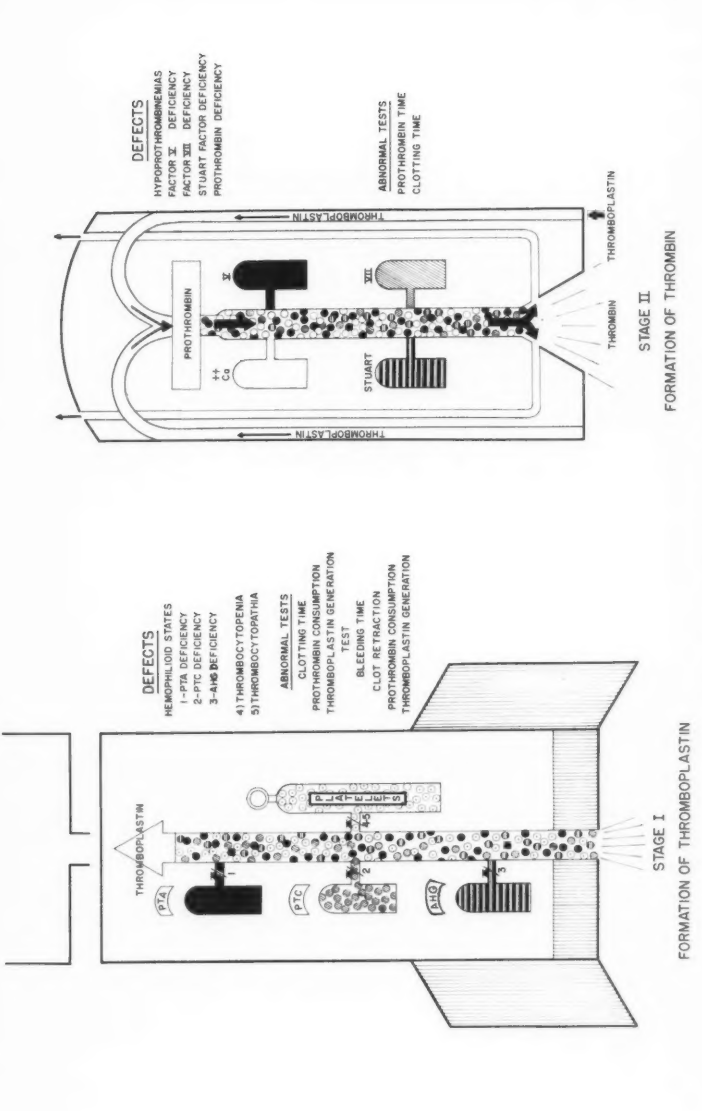

Figure 2. The coagulation "rocket."

(excess prothrombin remains in the serum), and an abnormal thromboplastin generation test. Platelet insufficiency or defect also impairs the latter 2 tests, but in addition gives rise to an abnormal bleeding time, poor clot retraction, and a positive tourniquet test.

Stage 2. Formation of Thrombin

Thrombin converts fibrinogen to fibrin in the final stage of coagulation, but thrombin itself does not exist free in plasma. It is derived from prothrombin, which exists probably as a homogeneous substance, a plasma globulin. Current evidence suggests that a number of preliminary reactions occur, the product of which activates prothrombin. This is similar to the first stage, for again a series of reactions is necessary to form an active substance. Initially, it was believed that thromboplastin and calcium activated prothrombin. Later, it was found that other factors—factor V and factor VII (the labile and stabile conversion factors), and Stuart factor—were essential before appreciable prothrombin conversion occurred.[17–19]

$$\text{prothrombin} \xrightarrow[(Ca^{++} + \text{thromboplastin})]{(\text{factor V, factor VII, Stuart factor})} \text{thrombin}$$

Factor V and factor VII are formed in the liver,[6] and are involved in most abnormalities attributed previously to prothrombin deficiency. Stuart factor is a more recent discovery. Lack of it produces a hemorrhagic diathesis, clinically indistinguishable from factor VII deficiency. In fact, the first case reported had been classified previously as a factor VII deficiency.[19] The metabolism of these plasma factors is not known definitely, but recent studies [20, 21] showed that hepatic mitochondria possess the ability to produce prothrombin in a cell-free system containing aged serum. The latter contains appreciable quantities of factor VII, which, unlike prothrombin and factor V, is not consumed during coagulation. As prothrombin was formed in the serum, factor VII decreased. Hepatic mitochondria from rats on Dicumarol failed to do this in a similar system, even after the addition of vitamin K. Fresh hepatic mitochondria produced factor VII even in plasma devoid of both factor VII and prothrombin.[20,21] Speculations resulting from these observations are notable, but beyond our present scope of interest. However, the fact that a normal level of factor VII occurs in congenital hypoprothrombinemia suggests that prothrombin and factor VII are independent substances that may be interconvertible.

A prolonged 1-stage plasma prothrombin time is characteristic of second-stage defects. Each factor in the prothrombin-thrombin equation is necessary for prothrombin activation. Lack of any single

factor impedes prothrombin conversion; incomplete conversion of prothrombin is the result and an excess of prothrombin remains in the serum. Hence, an abnormal prothrombin consumption test—in reality a 1-stage prothrombin time performed on serum, to which a source of fibrinogen has been added—is obtained. Factor V and Stuart factor also influence the conversion of prothrombin as well as the formation of thromboplastin—consequently a deficiency of either leads to impaired prothrombin activation.

Stage 3. Formation of Fibrin

The last phase of coagulation—the enzymatic conversion of fibrinogen to fibrin, the only visible phase of coagulation—serves as the indicator for all clotting tests performed in the laboratory. Thrombin, a proteolytic enzyme, has the ability to split the fibrinogen molecule. In the first phase of fibrin formation, a highly charged soluble peptide is removed from the fibrinogen molecule, leaving a molecule of fibrin. The molecule of fibrin is less highly charged than fibrinogen and the fibrin monomer undergoes polymerization, a process independent of thrombin. Linking of fibrin molecules to form solid fibers may be due to electrostatic forces following the removal of the highly charged peptide,[22] or to the formation of hydrogen bonds.[23] The reaction may be summarized by the following equations:

$$\text{fibrinogen} \xrightarrow{\text{thrombin}} \text{fibrin monomer} + \text{peptide}$$

$$\text{fibrin monomer} \longrightarrow \text{fibrin polymer}$$

$$\text{fibrin polymer} \xrightarrow{\text{calcium} + \text{fibrin-stabilizing factor}} \text{physiologic fibrin}$$

Although the final result is the formation of physiologic fibrin and deposition of a fibrin layer at the appropriate bleeding point, the amount of fibrin formed and eventually deposited is also influenced by fibrinolysis.

The fibrinolytic system is as complex as the blood-clotting system and resembles the coagulation mechanism in that 2 means of activation are provided. Plasminogen, or profibrinolysin, exists in the plasma as the inactive precursor of plasmin, or fibrinolysin. It may be activated by a tissue or a plasma activator.[24] The physiologic fibrinolytic system is influenced by the neuroendocrine system. Pituitary thyrotropic and somatotropic hormones promote fibrinolysis and the adrenocorticotropic hormone inhibits it. Circulating antifibrinolysins can also be demonstrated and play a role in the normal regulation of hemostasis.

HEMOSTATIC DISEASES

Study of the hemorrhagic diseases is handicapped by lack of exact quantitative methods for the determination of the clotting factors. Most tests are semiquantitative and not specific for a single factor. For this reason, a battery of tests is essential for adequate diagnosis of these diseases. Table 2 lists a number of tests applicable to the various primary hemorrhagic disorders.

Table 2. ***Common abnormalities in primary hemorrhagic disease***

Disease	*Tests**							
	Bl. T.	*T.T.*	*Pl. C.*	*Cl. ret.*	*C.T.*	*Prot. cons.*	*T.G.T.*	*Pro. T.*
Capillary disorders	+	+				+	+	
Thrombocytopenia	+	+	+	+		+	+	
Thrombocytopathia	+	+		+		+	+	
AHG deficiency					+	+	+	
PTC deficiency					+	+	+	
PTA deficiency					+	+	+	
Hageman factor deficiency					+	+	+	
Prothrombin deficiency					+			+
Factor V deficiency					+	+	+	+
Factor VII deficiency					+			+
Stuart factor deficiency					+	+	+	+
Afibrinogenemia					no clot			no clot

*Bl. T. = Bleeding time
T.T. = Tourniquet test
Pl. C. = Platelet count
Cl. ret. = Clot retraction
C.T. = Clotting time
\+ = Abnormal test
Prot. cons. = Prothrombin consumption
T.G.T. = Thromboplastin generation test
Pro. T. = Prothrombin time

Capillary Disorders

Vascular purpura. Hereditary hemorrhagic disorders involving capillaries are an ill-assorted group.[25–30] Scanty information is available on patterns of inheritance, diagnostic terms are confusing, and in many case reports the defect in the hemostatic mechanism lacks definition. In a recent survey of the field, Valberg and Brown[25] have attempted to clarify this situation. Capillary disorders may be pure or complicated by deficiencies of plasma factors. In the majority of cases, the tourniquet test is positive but other tests of coagulation give normal values.

Capillary disorder with prolonged bleeding time. Numerous titles have been bestowed on this condition, such as athrombopenic hemorrhagic purpura, thrombasthenia, hereditary pseudohemophilia, von Willebrand's diseases, pseudohemophilia A, and others. Bleeding

occurs early in life and may be severe. Ecchymosis, epistaxis, and oozing are troublesome, and excessive bleeding usually occurs after operations or dental extractions. Both sexes are equally affected and the disorder appears to be transmitted as a simple dominant gene.[25] In half the cases, the tourniquet test is positive and the bleeding time prolonged. Platelet counts are normal and the platelets are normal in appearance. During a hemorrhagic crisis, prothrombin consumption may be abnormal.

Capillary disorders associated with coagulation defects. Again a confusion of terms describing this type of defect exists. It has been called pseudohemophilia B, vascular hemophilia, hemophilia occuring in the human female, von Willebrand's disease, hereditary pseudohemophilia, Willebrand-Jürgens thrombopathy, and deficiency of antihemophilic factor A associated with a vascular disorder. The advent of more refined laboratory technics has dispelled much of the confusion surrounding these conditions. Capillary disorders have been reported in association with PTC deficiency,[28] AHG deficiency,[25] congenital factor VII deficiency,[29] congenital afibrinogenemia,[25] and platelet defect.[30] Capillary disorder with AHG deficiency is the most frequently encountered of this group. In the family studied by Valberg and Brown,[25] the disorder was transmitted as a dominant, independent of sex. The tendency to bleed appeared in childhood, and prolonged bleeding followed trauma or surgery. Easy bruising, epistaxis, and even hemarthrosis may occur. A variable prolongation of the bleeding time occurs and the tourniquet test also varies. The associated AHG or PTC deficiency impairs thromboplastic generation, and the clotting time and prothrombin consumption are abnormal. The prothrombin time is abnormal in those patients who have the capillary defect combined with factor VII deficiency. Johnson, Monto and Caldwell [30] studied a group of these patients in whom the associated defect was inability of the platelets to release platelet cofactor 3.

Defects in Thromboplastin Formation (Stage 1)

Thrombocytopenia. This may be congenital or acquired. The congenital type is a rare entity sometimes observed as a familial trait. Thrombocytopenia of the newborn infant has been associated with idiopathic thrombocytopenia in the mother, as a platelet antigen-antibody reaction analogous to erythroblastosis. The acquired type is the most common hemorrhagic disorder. It may be acute or chronic, idiopathic or secondary to other disease. Differentiation is often difficult and caution is necessary before applying the term "idio-

pathic," particularly to the acute thrombocytopenic purpura of childhood. Acute thrombocytopenic purpura may follow rubella,[31] mumps, or even the common cold.[32] In childhood it tends to be a self-limited disease, only occasionally becoming chronic. In the adult, the chronic variety predominates.

Secondary thrombocytopenic purpura may develop in the course of many diseases or their treatment. Infection, irradiation, drugs, blood dyscrasias, hepatic disease, lupus erythematosus, sprue, and pernicious anemia are some of the conditions in which it is observed. The thrombocytopenia may be caused by excessive destruction of platelets, often an immunologic reaction, or caused by depression of megakaryocytic activity within the bone marrow.

In thrombocytopenia, the platelet count is the *sine qua non* in diagnosis. The bleeding time is often abnormal, the tourniquet test positive, and clot retraction poor. When the platelet count is below 50,000 per cu mm, the prothrombin consumption and thromboplastin generation tests are abnormal, for platelets are essential in the first stage of coagulation.

Hemophilioid states. Hemophilia was considered a single disease until 1953, when White and associates [33] described a patient with the clinical and coagulation abnormalities of hemophilia, whose blood corrected the clotting defect of a true hemophiliac. The factor responsible for the correction was designated plasma thromboplastin component (PTC). In the same year, Rosenthal and associates [34] studied a family with a similar disorder, but blood from their patients corrected both the clotting defect of hemophilia and PTC deficiency. This third factor was called plasma thromboplastin antecedent (PTA).

The hemophilioid states can be differentiated even without employing blood or plasma from patients with specific defects. Normal plasma contains AHG, PTC, and PTA, and will correct a deficiency of any of these factors. AHG is consumed when blood or plasma clots, and barium sulfate will absorb PTC from serum or oxalated plasma. Normal plasma on aging loses its AHG. The 3 hemophilioid states can be differentiated by using plasma or serum (table 3). A simple test to diagnose classic hemophilia, described recently by Didisheim,[35] takes advantage of the fact that disodium ethylenediaminetetraacetic acid (Na_2 EDTA) selectively removes AHG from whole blood.

Hageman factor, a recent discovery, produces a "test tube" hemophilia.[36] The clinical features of the hemophilioid states are absent and hemorrhage does not occur, despite abnormal tests in vitro. An abnormal whole-blood clotting time and impaired thromboplastin generation are found, but prothrombin consumption may be normal.[37]

Table 3. *Differentiation of hemophilias**

Type of hemophilia	*Fresh normal plasma*	*Aged normal plasma*	*$BaSO_4$ absorbed normal plasma*	*Normal serum*
Classic or AHG deficiency	Yes	No	Yes	No
PTC deficiency	Yes	Yes	No	Yes
PTA deficiency	Yes	Partial	Partial	Partial
Hageman deficiency	Yes	Yes	Yes	Yes

* Corrective effects on the clotting time and prothrombin consumption: 1.0 ml of patient's blood added to 0.1 ml of reagent.

Hageman factor deficiency is a unique clotting entity that we have included with this group because of the similarity of the clotting defect in vitro.

Defects in Thrombin Generation (Stage 2)

The 4 deficiencies classified under second-stage defects, factor V, factor VII, Stuart factor, and prothrombin, are characterized by a common abnormal laboratory finding, a prolonged 1-stage prothrombin time.

Factor V deficiency (*parahemophilia*) occurs as a rare hereditary disease or as a complication of severe hepatic disease. The inherited deficiency appears to be a dominant trait involving both sexes.[38] The type of bleeding encountered is seen in all "hypoprothrombinemias," namely, bleeding into the skin, mucous membranes, and muscles. Petechiae and intra-articular hemorrhages are seldom encountered.

Factor VII deficiency may be congenital or acquired. Congenital factor VII deficiency occurs as a trait with incomplete dominance.[6] Acquired deficiency of this factor is found in many pathologic conditions. It is decreased in the blood of the newborn infant and by Dicumarol and related anticoagulants.

Stuart factor deficiency, another rare disorder, is inherited as a highly penetrant, incompletely recessive autosomal characteristic.[39] Stuart factor levels are depressed by long-term anticoagulant therapy.

Hypoprothrombinemia may be congenital or acquired. The congenital type is rare. Acquired hypoprothrombinemia follows deficient absorption or utilization of vitamin K and is common to a wide variety

of diseases. Circulating levels of prothrombin are decreased by anticoagulants such as Dicumarol.

Second-stage deficiencies require a battery of tests for differentiation. Again their presence or absence in plasma or serum is helpful. Factor V, commonly termed labile factor because of its rapid disappearance from plasma at room temperature, is not present in serum. Factor VII (stabile factor) is present in serum as well as aged plasma. Barium sulfate treatment of plasma removes prothrombin, factor VII, and Stuart factor. Table 4 summarizes a manner by which second-stage deficiencies may be identified.

In addition to an abnormal 1-stage prothrombin time, factor V and Stuart factor deficiencies are characterized by deficiencies in the generation of thromboplastin and prothrombin consumption. This is because both influence the first as well as the second stage of coagulation.

Table 4. ***Differentiation of "hypoprothrombinemias"****

Type of deficiency	*Normal plasma*	*Serum*	*$BaSO_4$ plasma (fresh)*	*$BaSO_4$ serum (aged)*
Prothrombin deficiency	Yes	No	No	No
Factor V deficiency	Yes	No	Yes	No
Factor VII deficiency	Yes	Yes	No	No
Stuart factor deficiency	Yes	Yes	No	Yes

*Corrective effect of the 1-stage prothrombin time: 0.09 ml of patient's plasma plus 0.01 ml of the reagent used for correction.

Defects in Formation of Fibrin (Stage 3)

Afibrinogenemia. This defect occurs occasionally as a congenital abnormality. The bleeding manifestations are similar to those in hemophilia, though not as severe, and ordinarily only follow trauma. The acquired defect usually follows surgical procedures, particularly pulmonic or prostatic, or accompanies pregnancy complicated by amniotic fluid embolism, premature separation of the placenta, or prolonged retention of a dead fetus.

Totally incoagulable blood is encountered in only 2 conditions, afibrinogenemia and hyperheparinemia; in the latter, the blood clots after the addition of thrombin or thromboplastin. In afibrinogenemia, only the addition of fibrinogen can produce a clot. Electrophoretic analysis of plasma to confirm the absence of fibrinogen can

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be done or the concentration of fibrinogen in the plasma can be measured.

Fibrinolysis. An increase in circulating plasmin (fibrinolysin) occurs most commonly as a complication of hemorrhagic shock, carcinoma of the prostate, or transfusion reactions. A mild increase in plasma levels is, at times, observed in cirrhosis of the liver. Certain drugs, such as para-aminobenzoic acid or trypsin, and bacterial pyrogens increase fibrinolytic activity. Therapeutic fibrinolysis as an approach to the treatment of disease has been the subject of intensive investigation in recent years. Recently, plasmin has been advocated for the treatment of venous thrombosis.[40, 41]

In acute fibrinolysis there is severe bleeding from all surgical wounds and venipuncture sites. Bleeding occurs into the skin and from mucous membranes. In chronic fibrinolysis, the bleeding is less violent but is prolonged. Bleeding into the skin, hematuria, and melena are common.

Usually the coagulation tests are normal, but spontaneous lysis of the formed blood clot may occur. Fibrinolysin may be detected by euglobulin lysis, thromboelastography, a fibrin plate assay, or measurement of undigested fibrin after incubation.[42, 43]

SUMMARY

The process of hemostasis is reviewed. The primary hemostatic factors are described as essential to the cessation of bleeding before the secondary factors, namely coagulation, become effective. For teaching purposes, coagulation has been compared to a 3-stage rocket. The various hemorrhagic diseases affecting man are described, relating them to the 3-stage concept.

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Radiogram for Determination of Cardiac Output

Comparison With Evans Blue Dye Dilution Method

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ALTHOUGH THE ACCURACY AND USEFULNESS of the dye dilution method for estimation of cardiac output have been established for many years,[1, 2] this method has major disadvantages, especially that of requiring arterial sampling. The ideal method of cardiac output determination would be as accurate as dye dilution but more rapid and without inconvenience to the subject.

In 1949 Prinzmetal and co-workers [3] described a precordial recording of radioactive material as it traversed the heart and noted that the resultant radiocardiogram was similar to a dye dilution curve. Subsequently, Shipley and associates [4] used the radiocardiogram to obtain an estimate of cardiac output. This method has been studied further in several laboratories,[5–10] and was recently reviewed by MacIntyre and co-workers.[11, 12] In all cases the investigators found the technic accurate when compared to the Fick method or to radioisotope dilution curves determined by arterial sampling. It has also been reported [10–12] that in cardiac diseases with decreased output the method is still accurate.

In the present study, reduced cardiac output was produced in dogs by hemorrhage. The radioactive precordial detection method is compared to the Evans blue (T–1824) dye dilution technic before and after hemorrhage, in order to determine the accuracy of the method over a wide range of outputs.

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MATERIALS AND METHODS

Experiments were performed on 15 healthy mongrel dogs (mean weight 14.0 kg, range 7.2 to 22.7 kg). In 11 dogs measurements of cardiac output were made before and after hemorrhage to a mean arterial pressure of 60 mm Hg; and in 4 others, serial measurements were made without hemorrhage. Arterial pressures, hematocrits, and cardiac outputs by the T–1824 dye dilution technic are described elsewhere.[13]

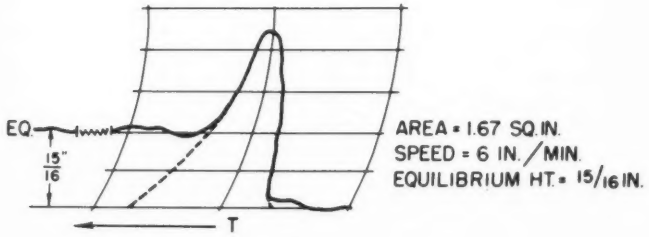

Figure 1. Radiocardiogram.

Radioiodinated serum albumin (RISA) was used for the isotope studies. A scintillation detector containing a ¾-inch diameter by ¾-inch thalliated sodium iodide crystal and a 2-inch lead collimator was connected to a Berkley (model 2850) counting rate meter. The meter was set at 10K range with a 2-second response time, and the output was recorded on an Esterline-Angus recording ammeter with a paper speed of 6 inches per minute (fig. 1). The radiocardiogram was extrapolated to the baseline visually and the area under the curve was measured with a planimeter. Equilibrium tracing was recorded 2 minutes after injection. Flow was calculated by the formula of Huff and associates:[5]

$$\text{Cardiac output (ml/min)} = \frac{\text{height of equilibrium} \times \text{paper speed per minute} \times \text{blood volume (ml)}}{\text{area of radiocardiogram}}$$

Plasma samples obtained before and 10 and 20 minutes after the injection and a diluted sample of the standard were counted in a scintillation well counter. The 10- and 20-minute plasma counts minus control counts were plotted on graph paper and the line extrapolated to the time on injection (t_o). Plasma volume was calculated in the following manner:

$$\text{Plasma volume} = \frac{\text{counts/ml/min of injected material} \times \text{volume injected}}{\text{plasma activity } t_o \text{ (counts/ml/min)}}$$

Blood volume was calculated from plasma volume and hematocrit.

The experimental procedure was as follows: Pentobarbital sodium (30 mg/kg) was given intravenously and the left femoral artery and vein and the right jugular vein were cannulated. The scintillation detector was placed over the apex of the heart. After a control sample of blood had been obtained, a measured quantity (approximately 1.25 μc/kg) of RISA was rapidly injected via the jugular vein, followed immediately by a 5-ml isotonic saline flush, and the radiocardiogram obtained. Then duplicate determinations of cardiac output by the dye dilution technic were immediately performed. For plasma volume determination, samples of blood were taken at 10 and 20 minutes following the injection of RISA. The animal was then bled to a mean arterial pressure of 60 mm Hg and the cardiac output determinations were repeated.

In order to evaluate the accuracy of the use of a 2-minute equilibrium value in association with blood volume calculated from the extrapolated t_o value, blood samples were obtained simultaneously with the recording of the equilibrium during 20 cardiac output determinations in a different set of animals. Two blood volumes were calculated as above in each instance, utilizing the plasma activity at t_2 for one and the extrapolated t_o value for the other.

RESULTS

The cardiac output values are shown in table 1. Before hemorrhage the cardiac outputs by RISA averaged 14.8 percent higher than the T–1824 measurements, and after hemorrhage the RISA value was higher by 9.5 percent. These differences are statistically significant ($P<.001$ and $P<.02$). The difference between 14.8 percent and 9.5 percent was not significant ($P>.2$). Figure 2 illustrates a scattergram of the combined data, resulting in a correlation coefficient [14] $r=+0.962$. The formula for the best fit straight line is $Y=0.88\ X-7$, where Y is the T–1824 value and X is the RISA value. Stated in another way, the RISA values were consistently 12 percent higher than the values for blue dye values. The standard error of the estimate of Y from X is ± 185 ml/min. Blood volumes calculated from the sample drawn at the time of the 2-minute equilibrium averaged 11 percent higher than the blood volumes calculated from the t_o values.

Table 1. ***Comparison of cardiac output determinations before and after hemorrhage by radioiodinated serum albumin and Evans blue dye methods***

Dog	*Before hemorrhage*				*After hemorrhage*			
	Cardiac output		*Difference*	*% Difference**	*Cardiac output*		*Difference*	*% Difference**
	RISA	*T-1824*			*RISA*	*T-1824*		
	ml/min		*ml*		*ml/min*		*ml*	
1	1261	1088	173	14.7	295	280	15	5.2
2	1690	1718	−28	−1.6	500	397	103	23.0
3	1280	785	495	47.9	430	428	2	0.5
4	4090	2985	1105	31.2	983	749	234	27.0
5	2115	2355	−240	−10.7	760	778	−18	−2.3
6	4002	4055	−53	−1.3	1003	940	63	6.5
7	3100	2455	645	23.2	494	454	40	8.4
8	2455	2415	40	1.6	630	660	−30	−4.6
9	1855	1560	295	17.3	520	425	95	20.1
10	1385	1239	146	11.1	592	500	92	16.8
11	4500	4505	−5	−0.1	1158	1118	40	3.5
12	2410	1840	570	26.8				
13	1195	1197	−2	−0.2				
	1235	1191	44	3.6				
	1092	1153	−61	−5.4				
14	1335	1151	184	14.8				
	1283	1149	134	11.0				
	1600	1180	420	30.2				
	1415	1122	293	23.1				
15	2525	2318	207	8.6				
	2530	1664	866	41.2				
	2620	1864	756	33.7				
	1942	1585	357	20.2				
			Mean 14.8				Mean 9.5	
			S. D. 15.6				*S. D.* 10.6	
			t=4.554				t=2.978	
			$P<.001$				$P<.02$	

*Calculated by the formula $\frac{\text{Difference} \times 2 \times 100}{\text{RISA C. O.} + \text{T-1824 C. O.}}$

DISCUSSION

The externally monitored RISA cardiac outputs and the Evans blue dye dilution outputs over a large range of values are highly correlated, as indicated by a correlation coefficient of +.962. However, this relationship does not indicate identity of the values. The RISA measurements are significantly higher than the T–1824 ones by about 12 percent. Other studies[5–12] report no significant difference between the measurements.

MacIntyre, Pritchard and Moir [11] have suggested that the blood volume must be calculated from a blood sample drawn at the time

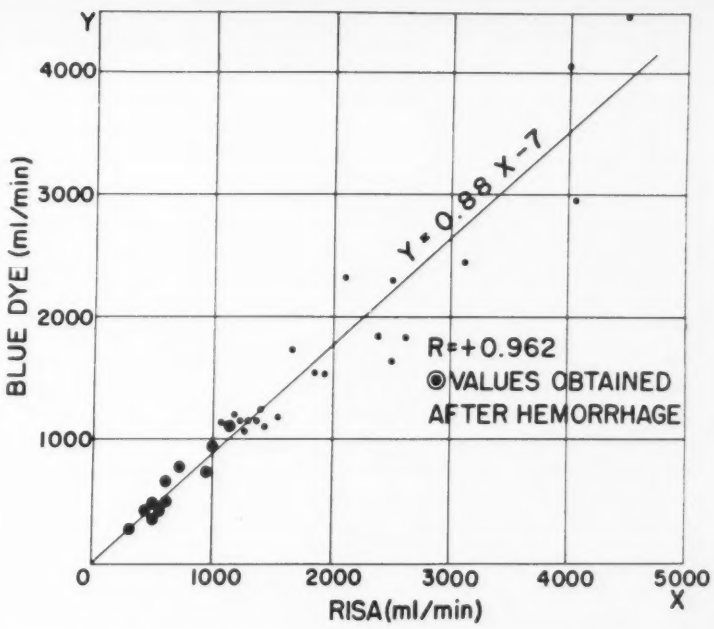

Figure 2. Comparison of cardiac output determinations before and after hemorrhage by radioiodinated serum albumin and Evans blue dye methods.

equilibrium is recorded, and that the accuracy or inaccuracy of this blood volume measurement is not important in the cardiac output determination. Blood volume was determined by the extrapolated t_o value in these experiments. If the assumption of MacIntyre and associates is correct, then an error would have occurred in the present experiments equal to the difference between the blood volumes calculated from the sample obtained at 2 minutes and that calculated from the extrapolated t_o. Measurement of this difference yields a value of 11 percent compared to a 12 percent difference in the cardiac output values. The similarity of the predicted error (from MacIntyre's assumption) and the observed error suggests that the assumption is correct and that the use of the blood volume calculated from a sample obtained at the time equilibrium is recorded would result in RISA cardiac output values not significantly different from those obtained by T–1824 dilution.

Advantages of the external monitoring method are: (1) Avoidance of arterial sampling simplifies the procedure and offers considerable

convenience to the subject studied. (2) It is not necessary to withdraw 50–100 ml of blood from the test subject, which under some clinical and experimental conditions may be injurious. (3) Finally, with the essential radioisotope equipment available, the RISA method is simple and rapid.

SUMMARY

A method of determining cardiac output by precordial monitoring of intravenously injected radioiodinated serum albumin (RISA) is described and compared to cardiac outputs measured by the Evans blue dye dilution method before and after severe hemorrhage. The isotope method yielded figures averaging 12 percent higher than the blue dye values, with a correlation coefficient $r = +.962$. This systematic difference between the methods was found to be related to technic, and a method of avoiding this difference is described. The RISA method avoids arterial sampling and loss of significant quantities of blood, and is simple and rapid.

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STRESS AND ITS HEADSTRONG OFFSPRING

It is so easy to bequeath an all-embracing word upon a wide variety of things and thus convince oneself that they all resemble each other closely. Are we not guilty of much the same thing if we use the word "stress" to embrace all the thousand natural shocks the flesh is heir to? The same word stress is applied to the deliberate crushing or burning of a limb in experimental work on anesthetized animals but is also used to cover the strain felt by a financier making money on the stock exchange. It seems likely that the reaction of most of us to having our legs crushed would be very different from our reaction to making money on the stock exchange. Not only has the word "stress" been allowed to run wild, but its headstrong offspring, the adaptation syndrome, has been given equal freedom to roam anywhere and lay claim to any unexplained illness that comes its way.—RICHARD ASHER: Making Sense. *The Lancet*, September 19, 1959.

Prolonged Intermittent Photic Stimulation

An Exploratory Study

MAJOR HAROLD S. ALEXANDER, USAF, MSC (RET.)
W. DEAN CHILES, PH. D.

THE HUMAN OPERATOR in current and future weapon and support systems may be exposed to intermittent light from a number of sources. These sources include radarscopes with high sweep rates, time-sharing displays, searchlights, and anticollision or other warning lights. The sun could provide high-intensity flicker when shining through propellers, when reflected from terrain or snow in low-level missions, and when shining through ports in a revolving space vehicle.

Typical reactions to intermittent illumination may be categorized as neutral, mild, or severe.[1] Neutral reactions include evidence of photic driving in the electroencephalogram (EEG) and the induction of visual sensations, such as apparent colors, moving patterns, and geometric designs. Nearly all persons exhibit at least some of these neutral reactions when exposed to such stimulation provided the light is sufficiently intense and of the proper frequency. Mild reactions include nausea, vertigo, visual hallucinations, headaches, ocular discomfort, and drowsiness, these responses being encountered in a rather small percentage of persons. Severe reactions are found in about 5 percent of known epileptic subjects, the total epileptic population constituting about 0.25 percent of the general population. Severe reactions include loss of consciousness and convulsions, generally followed by confusion and impaired thinking.

Most studies of the effects of intermittent illumination indicate that short periods of stimulation are adequate for the production of

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From the Behavioral Sciences Laboratory, Wright-Patterson Air Force Base, Ohio. WADC Technical Report 59–715. Major Alexander is now with North American Aviation, Inc., Missile Division, Downey, Calif.

reactions in susceptible subjects. The assumption is generally made that further exposure to the stimulus light will not result in either enhancement or a greater incidence of such effects. However, the stimulus period in these studies has not been systematically extended beyond about 60 seconds, a fact that raises a question of the utility of this assumption. Since many systems may be expected to subject the operator to such stimulation for relatively long periods of time, this exploratory study was initiated to examine the question whether, within a minimum of attention to selection, "normal" persons would develop serious behavioral disturbances during and after prolonged exposure to intermittent illumination.

METHOD

Subjects

The 4 male volunteers (military), 23, 27, 41, and 43 years of age, respectively, were in good general physical health and had negative medical histories with respect to neurologic symptoms, brain diseases, and epilepsy.

Apparatus

The apparatus employed in this study consisted of an electroencephalograph (EEG), stimulus lights with exciter devices, and a system of safety switches.

Four General Radio Strobolux lamps (type 648 A) were stacked in a symmetric rectangular array before the subject (fig. 1). The frequency at which the left upper light (light A) flashed was shifted, sometimes being set at 10 cps and at other times at 15 cps; the actual frequency selected depended on the relative dominance of high frequency versus alpha activity in the subject's preliminary EEG. The right upper light (light B) flashed at 10 cps, the left lower (light C) at 5 cps and the right lower (light D) at 15 cps. Each of the lights flashed continuously throughout the 2½-hour exposure period. The individual lights were triggered by separate mercury Electronic Company stroboscopes, which had been modified to permit lights A, B, and D to be maintained in synchrony with light C; thus, for example, the flash of light C coincided with every third flash of light D (15 cps) and with every second flash of light B (10 cps). The specifications published by the General Radio Company state that the flash duration of the Strobolux is from 15 to 50 microseconds (depending upon the frequency), with an accuracy of 1 percent; the peak

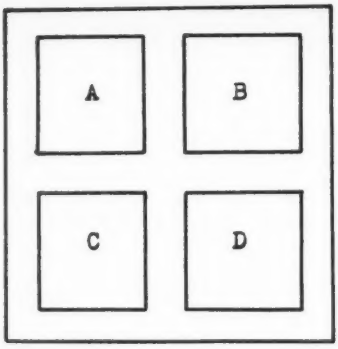

Figure 1. Arrangement of stimulus lights. The lights flashed at the following frequencies: A, 10 or 15 cps; B, 10 cps; C, 5 cps; D, 15 cps.

flash intensity at the frequencies used is specified to be 0.35 megacandle power. An oscilloscope driven by a photocell provided a technic for monitoring the stroboscope flashes and facilitated synchronization adjustments. The output of the photocell was also used to drive one pen of the EEG ink-writing oscillograph.

Procedure

The 4 subjects selected were given a detailed explanation of the purpose of the study and a description of the kinds of reactions that might conceivably occur, the probability of occurrence of any sort of severe reaction being estimated to be less than 1 in 10,000. A preliminary EEG, with and without the flashing lights, was recorded and analyzed. All 4 subjects exhibited normal EEG's, no marked photic driving, and no adverse subjective or other effects.

A simple addition test, 6 forms of which were available, was given to the subject at 15-minute intervals during the exposure. The test consisted of rows of numbers that were to be added consecutively until the sum of the series in a given row was equal to an underlined number at the left of that row. One minute was permitted for each test. The test was started after initial EEG adjustments and recordings were completed and after the stimulus lights were turned on. Upon completion of the stimulus period (about 2½ hours) a final test was administered under normal illumination.

EEG Procedures

Bipolar electroencephalograms were recorded from the right and left occipital, parietal, and post-temporal areas of the brain on an Offner type D3 EEG, using Remond tripod electrodes.

The scalp of the subject was prepared for the electrodes by the thorough cleansing of the points of contact with acetone and by liberal application of electrode paste. The electrode resistances were checked periodically throughout the session and were returned to initial values by adding more paste when necessary.

The EEG activity was recorded and monitored continuously during the first 30 minutes of exposure. From that point on, 3- to 5-minute recordings were made at 20-minute intervals, with care being taken to insure adequate samples of both "eyes open" and "eyes closed" activity. The EEG was again recorded continuously during the last 15 minutes of exposure and for 5 minutes following the extinction of the lights.

RESULTS AND DISCUSSION

The verbal reports indicated that the reactions of all 4 subjects were strictly neutral; the reports described the perception of colors, geometric designs, and patterns of movement. All subjects reported that the flashing of the lights seemed to become less compelling as time proceeded.

Of the 4 subjects, 3 reported becoming drowsy during the course of the exposure, and evidence of the reported drowsiness was apparent from time to time in the EEG records. This factor could have resulted from the nature of the situation and the general boredom one would expect it to produce.

After about 1 hour of exposure to the lights, all 4 subjects showed definite evidences of photic driving. In 2 subjects there was enhancement of 15 cps and 30 cps activity; a third subject showed a build-up of 10 cps activity; and the fourth subject showed an increase at 10 cps and 30 cps. The record of this latter subject is presented in figure 2; it was selected for presentation because of the fact that, although the driving effect was less pronounced for this subject than for the others, it is still quite evident. All records returned almost immediately to pre-exposure levels when the lights were extinguished.

The performance on the addition test showed no systematic trends as a function of length of exposure to the lights. However, performance was in general somewhat below the expected levels—probably as a result of the adverse lighting conditions, since the task was highly visual in nature. It should be emphasized that, because of the exploratory nature of the investigation, better measures of performance were not obtained.

It is concluded, within the limits imposed by the sample size, that "normal" individuals are resistant to the development of adverse

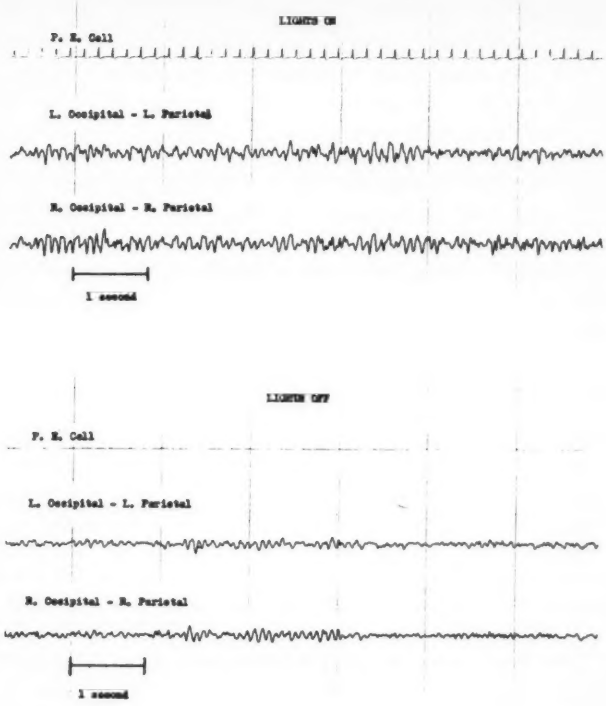

Figure 2. Samples of record for subject 4 taken after 2 hours and 25 minutes of continuous stimulation and immediately after extinguishing lights.

subjective or physical reactions when exposed to bright, flashing lights for relatively long periods of time. The status of the reported drowsiness is somewhat ambiguous in that there is good reason to believe that it would have developed in this sort of situation in the absence of the visual stimulation.

On the basis of a large quantity of clinical and experimental literature,[2] the following obvious recommendations can be made with respect to the selection of personnel who will be exposed to conditions similar to those employed in this study:

(1) The medical history should be negative as regards those neurologic symptoms or disorders associated with the various forms of epilepsy.

(2) The EEG should show no evidences of abnormalities of the kind commonly referred to as "paroxysmal activity."

(3) There should be no abnormal EEG responses during a 10-minute exposure to bright lights that flash at or near the fundamental EEG frequencies.

It is believed that the present study lends (at least limited) support to the last of these recommendations.

SUMMARY

In order to investigate the resistance of the human operator to effects of intense, flashing lights for prolonged periods of time, 4 subjects were exposed to very bright intermittent photic stimulation at 5, 10, and 15 cycles per second for a period of 2½ hours. None of the subjects suffered any adverse subjective or behavioral effects, although all became somewhat drowsy from time to time, presumably as a result of the boring nature of the situation.

After about 1 hour of stimulation, all 4 subjects showed definite evidences of electroencephalographic responses to the lights.

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EXTERIOR REDECORATION

Too much is written, and too much is published. I am dismayed to see the same material rewritten by the same authors published in as many as four different journals. To be sure, there may be rearrangements of paragraphs, and there is usually a rewording of the title, to confuse the index, but not the discerning reader. The order of the authors' listings is always changed. I would not examine here the many reasons why republication is so common a practice, but I admit to my suspicions that venality is among the motives.—LEONARD D. ROSENMAN: Hugh of Lucca and the Literary Virus. *The New England Journal of Medicine*, Dec. 24, 1959.

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Effects of Zero Gravity Upon the Cardiovascular System

Preliminary Observations

LEONARD J. STUTMAN, M.D.
LIEUTENANT ROBERT OLSON, USAF, MSC

ZERO GRAVITY of only limited duration and at only intermittent intervals can be achieved at present. The longest duration obtained, utilizing a C 131B Convair-type aircraft, has been approximately 15 or 16 seconds. Although longer periods of zero gravity, up to 1½ minutes, can be obtained with higher-performance aircraft, the size of the cockpit in these aircraft limits instrumentation of the subject.

It was the intention of this investigation to measure some of the physiologic changes, utilizing a simulated model, that a human would experience upon entry into and return from a zero gravity field. Complete information regarding physiologic changes in the circulatory system during man's stay in zero gravity fields in space [1,2] will be impossible to obtain on earth. It is, however, possible to simulate conditions of entry into zero gravity and return from zero gravity to standard gravity.

It has been demonstrated [3] that changes in cardiac rate and syncopal episodes can be produced in about 20 percent of apparently normal men by acute changes in position on a tilt table. It was therefore decided to place such a tilt table under conditions of zero gravity, in order to (1) afford a stable point to measure a man's attitude and G fields during entry and reentry; (2) facilitate instrumentation for

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measuring a number of variable factors; and (3) present a possible device for crew selection.

METHOD

At the time the study was undertaken, as already mentioned, the longest duration of zero gravity obtained utilizing a large aircraft (C 131B Convair) was approximately 15 or 16 seconds. Longer periods—up to a minute or more—could be obtained with high-performance aircraft, but the limitations of cockpit size would handicap instrumentation of the subject. Therefore, a tilt table (fig. 1) equipped with suitable devices for recording acceleration, respiration, simultaneous electrocardiographic leads, blood pressure, and plethysmographic blood volume changes was installed in the afterbay of a Convair 131B aircraft. The tilt table was used not only to determine horizontal or other placement, but to assure fixed attitude so that body movements would not alter strain-gage readings. Blood pressure determinations were taken in a pressurized cabin with an aneroid apparatus to rule out inertial inaccuracies. A continuously recording 12-channel recorder with individual pre-amp systems was used. Standard electrocardiographic leads were recorded with a Hyland

Figure 1. Tilt table.

galvanometer. These were damped so that aircraft vibrations did not affect the recordings materially. Strain gages were attached to the limbs in such a way that the forces of vertical acceleration would not affect the readings—a positive deflection indicating further stretching of the strain gage and a downward deflection indicating a decrease.

Four human subjects were used after careful investigation to exclude prior history of cardiovascular disease. One subject was a high-performance pilot, another was a medical service officer, and 2 were enlisted personnel.

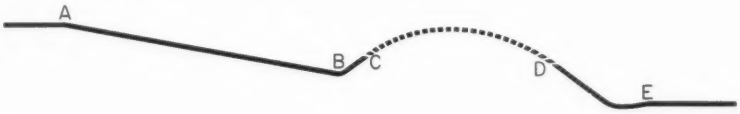

Figure 2. Aircraft starts 10° dive at 12,000 ft, at "A," picks up speed to 250 knots; at "B" pulls up to 2½ G at a 35° climb; pushes over at "C," where the subjects instantly experience zero gravity and maintain this until "D," when aircraft goes into a 35° dive; at "E" the plane ends a pull-up of 2 G and 250 knots air speed and is in level flight at 10,500 ft.

The course of the plane is indicated by figure 2. The plane picked up acceleration to 2½ G, the nose was then elevated, and a Keplerian-type parabola was described, during which zero gravity was experienced. The subject was placed on the tilt table, the first position being horizontal with respect to the earth. In all, 3 positions relative to the thrust of gravity—horizontal or transverse, perpendicular, and 45°—were utilized. More than 250 dives were made to insure complete and accurate recordings, including at least 2 Keplerian parabolas for each person in each position.

RESULTS

Consistent changes were observed in all persons (figs. 3 and 4; table 1). An abrupt decrease in heart rate occurred at the point of change from positive to zero gravity, and an abrupt increase from zero to positive gravity (table 1). These changes may be noted most clearly in figure 3, where all channels except lead I and the 2 accelerometers are turned off. Zero gravity starts at "2" and begins to become positive at "4." The abruptness of the change is significant and cannot be due to artifact. The timing of the lines is 10 per second, from which the rate of change can be calculated (table 1). This varied in range from 8:5 to 2:1 and in one subject dropped from 80 to 40 on entry—indeed a marked change.

Table 1. ***Average values in 4 subjects of heart rate, blood pressure, and strain-gage deflections in the horizontal or transverse position***

Measurement	*Level flight (2 min)*	*Acceleration 2.5 G (10–15 sec)*	*Zero G (15 sec)*	*Acceleration 1.5–2 G (10–15 sec)*	*Level flight (2 min)*
Average R-R rate	74	97	50	62	79
Average B.P. (mm Hg)	118/80	(*)	110/70	(*)	125/80
Direction of strain-gage deflection	none	none	+++	+	none
			15 sec		

*Not obtainable.

Blood pressure determinations were taken directly with a cuff, and 2 measurements were obtained during each zero gravity field. Although blood pressure rose during the positive G acceleration, there was shown to be a consistent drop in both systolic and diastolic pressures during the experience at zero gravity. There was again a rise during the subsequent positive G effect. Quantitatively the decrease at zero G was from 5 to 10 percent. Since the direction of change was consistent even when the position of the subject was altered with respect to the direction of acceleration, it is felt that this change is not an artifact.

Strain-gage plethysmography recorded changes in limb volume. All subjects experienced an increase in the peripheral blood volume in the zero gravity field, as indicated by line 1 in figure 4. Positive

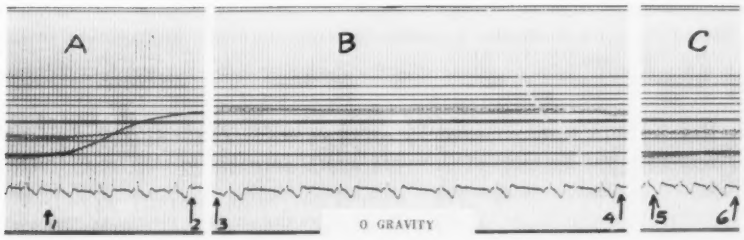

Figure 3. Slowing of the pulse rate with the subject in the horizontal or transverse position. Three channels of this 12-channel recorder are being utilized. The upper 2 channels represent vertical and horizontal accelerometers and the lower channel is the mirror image of standard lead I. (A) In the 10-degree dive between 1 and 2 the pulse rate is 71. (B) In the zero gravity period between 3 and 4 the pulse rate has slowed to 46. (C) After the return to positive gravity (1 G) and level flight the rate is 80. Similar patterns were obtained with the other subjects.

strain-gage deflection appears after the entry into zero G (at "D") and the gage begins to go down as the aircraft starts to go back into the positive G field (at end of "G"). Motion pictures taken of the subject show clearly the swelling of the face, which appears in the first positive G thrust and is maintained during the zero G phase. It is conceivable that this is a residual from the loading that occurred during the positive G thrust, but the fact that it begins to decrease during the second positive G phase seems to indicate that it is indeed an effect related to zero G.

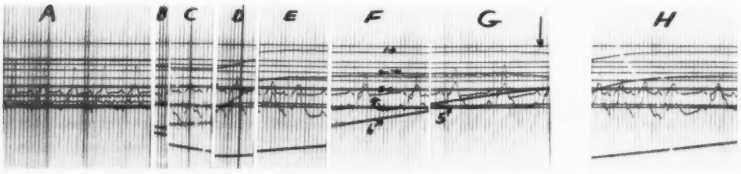

Figure 4. In continuous sections of a double parabola, the effects of zero gravity on peripheral pooling, pulse rate, and electric position of the heart are shown. (1) Strain gage around legs. (2) and (5) Accelerometers. (3) and (4) Simultaneous leads, standard lead I and V_2. (6) Course of the aircraft. The subject is in the horizontal (transverse) position and the following takes place: (A) the plane is in level flight; (B) and (C) 10-degree dive; (D) beginning of pull-up; and (E) pushing over into the zero gravity field (E–G).

Note the positive increase in strain-gage deflection, indicating increased blood volume in the extremities. The simultaneous leads "3" and "4" show no change except slowing of the rate. The arrow at the end of "G" points to the beginning of the 35-degree dive and 2 G pull-up. (H) Section from a second successive parabola showing the same information as in "D," "E," and "F."

Respirations were counted by an observer. There appeared to be a decrease, but because of the very short duration of the zero G field it was not possible to ascertain this statistically.

Subjects were changed from vertical to horizontal position, via the tilt table, while in the zero gravity field. This did not affect heart rate, blood pressure, blood pooling effect, or the electric position of the heart. However, in relation to position certain phenomena were observable. Maximum slowing of heart rate on entry into zero G in a given subject always occurred when he started in the horizontal (transverse) position. Likewise on reentry, the maximum speeding-up would occur with the subject in the vertical (perpendicular) position.

Peripheral pooling was most marked when the subject started in the perpendicular position.

DISCUSSION

The results recorded here may indicate a phenomenon of the zero gravity field—namely, that in this situation the heart rate and blood pressure decrease. Theoretically this is to be expected, because less work is demanded, not only of the subject, but probably of the heart. These results may indicate that if man remains in a zero gravity field, his processes will slow down—perhaps as a result of the decreased demand for energy that this environment places upon him.

It is well known [4] that marked changes in both musculature and skeletal structures take place even under normal gravity whenever energy demands diminish. On this basis one can expect a decrease in the venous return in a man maintained for any substantial length of time in zero gravity and additional disabilities when time comes for his reentry into the earth's gravitational field. Although a person may be able to sustain alterations that occur in passing from positive to zero gravity, there will be more difficulties on reentry, in respect to the sudden changes that the cardiovascular system will have to endure. This raises the practical question of providing some device for the benefit of the future astronaut to provide for the maintenance of the venous return to the heart. A gastrocnemius muscle stimulator or general bodily exercise of some sort may be considered as devices to meet this need. Lastly, it would seem that the decelerative force of reentry should, by necessity, be very much less than the maximum accelerative force, to permit safe reentry.

Further work with more subjects is under way to clarify these problems.

SUMMARY

Some preliminary investigations of the effects of zero gravity upon the cardiovascular system reveal a pronounced slowing of heart rate, a slight diminution of blood pressure, and a tendency to peripheral pooling subsequent to the positive G load. Position in the zero G field does not seem to affect the cardiovascular system. Hypotheses are proposed for the potential circulatory difficulties that will hamper a person's return to earth.

ACKNOWLEDGMENT: The authors wish to thank Dr. Lida G. Gottsch for her excellent editorial review.

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THE PRESERVATION OF HUMANITARIANISM

Society has given our profession the highest score in humanitarianism and the lowest in cynicism as compared to any other calling. In the minds of the laity the image of the physician remains that of a benefactor of humanity. He is still heir to priestly tradition and continues to be accorded a respect and awe which is unique in our culture. How long this condition will prevail will depend upon many factors but also upon ourselves. There is a growing turmoil in the world which is reflected in our society and in our lives. Powerful forces are at work which tend to undercut the societal role presently held by the physician. Our profession must remain alert and lead the way to a searching scrutiny of their origin and expose the selfish interests that promote them. Selfish interests are cynical, always in conflict with humanitarianism.—LOUIS H. NAHUM: Medical Education, The Physician and Society. *Connecticut Medicine*, April 1959.

Clinicopathologic Conference

Young Woman With the Blue Nose

Brooke General Hospital, Fort Sam Houston, Texas

A 35-YEAR-OLD WOMAN, a printing-plant worker, was admitted to the hospital on 14 December because of "turning purple," with onset that morning.

Two days before admission, while at work in the printing plant, she had become weak and had been excused early; however, she went shopping before going home and to bed. The next day she had to stay in bed on account of weakness and shortness of breath; yellowing of the eyes was also noted, as was lower abdominal cramping. Pain-killing pills bought at a local drugstore were taken at 1400 and 1800 hours.

On the morning of admission she awoke with marked weakness and shortness of breath. In addition, when her children saw her they began to cry because she looked so strange; her skin had a diffuse reddish purple color, and her nose, cheeks, and hands and feet were dark blue. She had no pain and a menstrual period seemed to be proceeding normally.

She saw a local physician, who gave her an injection of vitamin K plus another injection, and referred her for immediate hospitalization. Past history revealed her to have been in robust health. She had not seen a physician from the time of her last pregnancy 8 years before, until 4 days prior to admission, when a physical examination had apparently revealed that she was fit.

Review of systems revealed no particular problem, except that menses had been slightly irregular for the past year; her last menstrual period was reported to have been 20 November.

From the Pathology Service, Brooke General Hospital, Fort Sam Houston, Texas, Col. George J. Matt, MC, USA, chief. Brig. Gen. Clement F. St. John, MC, USA, former commanding general, was succeeded by Brig. Gen. Robert B. Skinner, MC, USA, on 1 Oct. 1959. Case is from the files of the Bexar County Medical Examiner, Robert Hausman, M.D.

Physical Examination

The patient was a well-developed and well-nourished woman with acute dyspnea. Temperature was 94.6° F; pulse was 120 per minute; respirations were 48 per minute; and blood pressure was 120/70 mm Hg. The skin had a diffuse reddish purple color, and the hands and feet were cold and blue. In addition, the nose was a deep blue color and the lips and tongue were also blue, but to a lesser degree. The eyes were markedly jaundiced, but the pupils were equal and round. The chest was clear. Abdominal examination elicited no pain or tenderness; blood was noted on the perineal pad. Neurologic examination was grossly physiologic except for diminished sensation.

Laboratory Studies

Hemoglobin was 5.9 grams per 100 ml; hematocrit was 7 ml per 100 ml; and white cell count was 28,000 (segmented neutrophils 83 percent, band neutrophils 3 percent, metamyelocytes 1 percent, and lymphocytes 13 percent). Prothrombin time was 29 seconds (control, 15 seconds).

Portable chest roentgenogram showed no gross abnormalities.

Course in Hospital

Considered to be in critical condition, the patient was admitted to a medical ward. Nasal oxygen administration caused her hands to assume a pinker color, but her respiratory distress continued. When blood analysis was performed, the laboratory technician reported that the serum had a port-wine color. A consultant recommended antibiotic therapy, and administration of aqueous penicillin, 1,000,000 units intramuscularly every 4 hours, and streptomycin, 0.5 grams intramuscularly every 6 hours, was initiated, along with a 300-mg intramuscular injection of cortisone acetate. Two hours after arriving on the ward, while apparently resting comfortably, the patient suddenly lapsed into coma and died a few minutes thereafter.

DISCUSSION

DR. BLOUNT:* The case today involves a young adult woman, apparently quite well until within 3 days prior to her death. After a fulminant illness characterized by peculiar skin discoloration, shock,

*Col. Robert E. Blount, MC, USA, chief, department of medicine.

and an acute hemorrhagic process, she died rather suddenly. From the description of this peculiar discoloration of her skin, should we consider the possibility of an element of methemoglobinemia?

DR. SORENSEN:* If the pain-killing pills which she took were of the APC type, they contained phenacetin and acetanilid, both of which are incriminated in the development of methemoglobinemia. Although we do not know how many she took, the dosage may not be important. Fatal cases of poisoning have occurred with small doses, whereas 30 grams have been taken without fatal results. There is considerable individual susceptibility to these drugs but generally the dosage required to produce hemolytic anemia is much higher than that which will produce methemoglobinemia.

Regarding toxins associated with printing-plant work, talks with various printing plants in San Antonio indicate that aniline dyes are meagerly used, being found only in connection with colored pictures.

If the hematocrit is 7, the hemoglobin of 5.9 grams percent is greatly elevated out of proportion. If the usual acid-hematin method is used for hemoglobin determination, the methemoglobin would not be measured, and thus the stated values would seem to be even more out of proportion. I feel this patient has a hemolytic anemia with a superimposed methemoglobinemia.

DR. BLOUNT: The observation made by the laboratory technician that the serum was port-wine color is of vital importance. This is the simplest test that can be done to indicate the presence of hemolysis. The causes of hemolysis are almost legion. Wintrobe [1] gives the following classification of hemolytic disorders:

I. *Extracorpuscular causes*

- A. Acute hemolytic anemias due to immune body reaction
  1. Isoagglutinins anti-A, anti-B (transfusion reactions)
  2. Isoagglutinins anti-Rh, anti-Hr, Kell, Duffy, etc. (hemolytic disease of the newborn, "intragroup" transfusion reactions)
  3. Cold hemolysins (paroxysmal cold hemoglobinuria)
- B. Idiopathic acquired hemolytic anemias
- C. Secondary or symptomatic hemolytic anemias
  1. Hodgkin's disease
  2. Chronic lymphocytic leukemia, lymphosarcoma
  3. Disseminated lupus erythematosus
  4. Metastatic carcinomatosis
  5. Dermoid cysts
  6. Liver disease
  7. Thrombotic thrombocytopenic purpura

*Capt. Robert J. Sorensen, MC, USA, resident in medicine.

D. Infectious agents
  1. Malaria
  2. Bartonella (Oroya fever)
  3. Septicemia: *Clostridium welchii, Vibrio comma* (cholera), rarely others
  4. Viruses (atypical pneumonia, infectious mononucleosis)

E. Chemical agents
  1. Related to size of dose
    a. Phenylhydrazine
    b. Naphthalene
    c. Trinitrotoluene
    d. Benzene
    e. Acetanilid
    f. Phenacetin
    g. Aniline
    h. Methyl chloride
    i. Arsine
    j. Lead
  2. Depending on hypersensitivity
    a. Sulfonamides
    b. Quinine
    c. Pamaquine
    d. Primaquine
    e. p-Aminosalicylic acid
    f. Benzedrine
    g. Mesantoin
    h. Paraphenylenediamine

F. Physical agents (heat—severe thermal burns)

G. Vegetable and animal poisons
  1. Vegetable poisons
    a. Fava bean (*Vicia fava*)
    b. Castor bean (ricin)
  2. Animal poisons
    a. Snake venoms

II. *Intracorpuscular defects*

A. Hereditary spherocytosis (familial or congenital hemolytic jaundice)
B. Hereditary elliptocytosis
C. Hereditary nonspherocytic hemolytic anemias
D. Hereditary leptocytosis (thalassemia, Mediterranean anemia)
E. Sickle-cell disease
F. Other hereditary hemoglobinopathies (C, D, E, G, H, I, J, K)
G. Combinations of thalassemia and sickle-cell disease or other hemoglobinopathies
H. Paroxysmal nocturnal hemoglobinuria

DR. MENDEZ:* Concerning Oroya fever as a cause of hemolysis, the possibility does exist. The disease is, however, limited to 3 countries in South America—Equador, Colombia, and Peru. The old saying that the disease does not occur below the altitude of 9,000 feet has not proved true, for the cases in Colombia and Equador are at lower altitudes. The bartonella organisms attack the red cells, causing a fast and furious anemia. A fatal course ensues in 30 percent of cases, usually terminating in about 3 weeks. If not fatal, the disease usually goes into the verruca peruana phase. Although causing a hemolytic anemia, it also develops a macrocytic anemia, as opposed to this case.

*Capt. Enrique Mendez, Jr., MC, USA, resident in medicine.

Malaria is another case of hemolysis among the infections, but again this disease is rare outside of tropical zones.

DR. BLOUNT: Incidentally, malaria with blackwater fever still occurs quite frequently in Africa. Despite antimalarial suppressive medication, acute hemolytic episodes due to falciparum malaria still occur.

DR. AUSTIN:* Although the protocol indicates, by the patient's history, that she had had a normal menstrual period about 1 month preceding her admission and that she was apparently menstruating on admission, don't overlook the possibility of a criminal abortion. These patients are frightened and almost invariably will not give a correct menstrual history when first asked.

The woman died a relatively sudden death from some fulminating condition, a part of which was a profound hemolytic anemia. *Clostridium welchii* will definitely produce a hemolytic type of anemia.

Fortunately, from my standpoint, I have never had to treat this condition and must rely on the literature for comments. A very comprehensive review of this subject was presented at the First Armed Forces Seminar in Obstetrics and Gynecology held at this hospital in March 1952.

The typical clinical picture is quite similar to this protocol. The patient is usually alert but extremely ill and dehydrated. The pulse is rapid and weak and the blood pressure may be lowered. Occasionally there is dyspnea and jaundice. The urinary output may be decreased or absent. The jaundice may become quite marked, producing a bronze color. Nausea, vomiting, and diarrhea may be present. The fever, if any, is usually low-grade type. The patient complains bitterly of progressively excruciating uterine pain. The skin is cold and clammy and, in severe cases, cyanosis may be present. Pelvic examination reveals a foul vaginal discharge containing numerous gas bubbles and having a sweetish odor. There is usually only slight bleeding from the cervical canal. The vaginal mucosa may be green or black. Bimanual examination reveals extreme tenderness.

Because of the hemolysis there is usually a severe secondary anemia. As the disease progresses, there is first oliguria with hemoglobinuria, then anuria. The patient develops progressive dyspnea and cyanosis with jaundice. She is characteristically mentally alert until death. If not vigorously treated, about one third of these patients die within 48 hours, and another 50 percent by the eighth day.

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*Maj. James A. Austin, MC, USA, assistant chief, obstetrics and gynecology service.

If this is a septic abortion, and I believe it is, it is doubtful that even proper therapy would have saved her, since she died in about 2 hours. *If a pelvic examination had been done, in spite of the "normal" menstrual period, the diagnosis might have been evident, and prompt and vigorous therapy might have altered the outcome. There should be very few occasions in medicine for the note "pelvic and rectal deferred" on the chart, and in those few it should be done as soon as circumstances permit.*

DR. KARR:* Does not hypothermia tend to rule out an infectious etiology here in favor of a toxic origin?

DR. BLOUNT: The absence of fever is a point against infection, but in some septic abortions with fulminant infection, only a low-grade or no fever may be seen.

DR. TESCHAN:** This patient had quite possibly developed acute renal failure, even though no information is given about urinary flow or color, or findings in the urinary sediment. Acute hemolytic episodes are, of course, known to produce acute tubular necrosis (lower nephron nephrosis). On the other hand, attempts to reproduce this lesion experimentally by large oxyhemoglobin injections have failed, suggesting that more than "simple" hemolysis of red cells is needed.[2] A simple calculation, assuming 50 kilograms of body weight, no changes in total blood volume, and an initial hemoglobin level of 14 grams per 100 ml, suggests that the peak plasma hemoglobin concentration in this patient might have approached 9,000 mg percent. This is 40 to 50 times the level which has been associated with only transient oliguria in man, but implies no higher hemoglobin load than was achieved in the experiments with oxyhemoglobin. It is possible that human kidneys could be damaged by this dose level. Furthermore, a severe renal lesion can occur if an appreciable amount of the pigment is methemoglobin instead of oxyhemoglobin. No data are provided in the protocol regarding this possibility.

The calculation:

1. Initial hemoglobin level (assumed):		140 gm/l
less final hemoglobin level (protocol):		50 gm/l
	=Hemolysis	90 gm/l

2. Patient weighed 50 kg. Total blood volume (8%) = 4.0 l

*Capt. Walter J. Karr, Jr., MC, USA, resident in medicine.
**Maj. Paul E. Teschan, MC, USA, chief of renal section, surgical research unit, Brooke Army Medical Center.

3. Total acute load of hemoglobin (assuming no change in blood volume):
   90 gm/l×4 l=360 gm hemoglobin
   360 gm÷50 kg=7.2 gm/kg
4. Plasma hemoglobin after hemolysis:
   hematocrit=7%; plasma volume=93%×4.0 l=3.72 l
   360 gm÷3.72 l=90.32 gm/l or 90,320 mg/l or 9,032 mg per 100 ml

DR. BLOUNT: Certain diseases such as atypical pneumonia and infectious mononucleosis are sometimes associated with acute hemolysis with an acute hemolytic process.

DR. MOSER:* I have never seen a hemolytic episode of this severity with any virus or virus-like states. Of the various possibilities I have seen only the Marchiafava-Micheli syndrome (paroxysmal nocturnal hemoglobinuria) become this devastating with this rapidity. Along this line, the identification of primaquine-sensitive erythrocytes is being recognized. This has been seen in Negroes. Apparently these red blood cells are quite capable of normal function under any circumstances unless they are placed in contact with primaquine and some of the aniline derivatives. It has been demonstrated that these red cells have an intrinsic enzymatic defect apparently in the carbohydrate cycle, which results in a reduction in reduced-glutathione content. This does not interfere with the integrity of the cell until the offending agent is added to the plasma. Then Heinz-body formation occurs and this is a prelude to dissolution of the cell. A similar mechanism is being postulated for favism, and this is reminiscent of the quinidine-hapten mechanism in platelet destruction.

DR. BLOUNT: Paroxysmal nocturnal hemoglobinuria (PNH) certainly is a strong possibility. The presence of a polymorphonuclear leukocytosis is rather inconsistent with PNH, however.

When such a set of symptoms or clinical findings appears, I am sure that a pediatrician would suspect toxic agents. What are such possibilities?

DR. GEPPERT:** In regard to erythrocyte defects, a recent report from Johns Hopkins [3] mentions a group of adult Negro women who were exposed to naphthalene in the form of moth balls, and subsequently developed a hemolytic anemia, apparently due to the interference in the intrinsic erythrocyte metabolism by the naphthalene.

Working backwards, it was discovered that newborn children have this same potential defect, hemolysis resulting if naphthalene exposure is allowed. Vitamin K, having a structure like naphthalene, will

*Maj. Robert H. Moser, MC, USA, assistant chief, department of medicine.
**Col. Leo J. Geppert, MC, USA, chief, pediatric service.

also produce hemolysis in the newborn. Several instances have been encountered in the nursery where vitamin K given to the mother was causing a blood disturbance in the child. In today's case, if such an erythrocyte defect existed, the slug of vitamin K she received would only have aggravated the situation.

DR. BLOUNT: Years ago when bismuth subnitrate was used in the therapy of diarrheas, severe toxic states with symptoms resembling this illness sometimes appeared due to nitrite poisoning.

DR. HEWITT:* Of the 3 major causes of anemia—bleeding, bone marrow depression, and hemolysis—the presence of hemoglobinemia indicates intravascular hemolysis in this case. To investigate this, the simplest thing to do would be to look at a blood smear; stippling or Heinz bodies would suggest a drug-dependent hemolysis. Culture technic would be needed for infections. Paroxysmal nocturnal hemoglobinuria is a strong possibility, although usually associated with leukopenia and thrombopenia. The Ham test would confirm the intracorpuscular defect, if another's serum caused additional hemolysis when the patient's serum had no effect on normal red cells. Since donor plasma does intensify hemolysis of a patient's cells in paroxysmal nocturnal hemoglobinuria, only washed donor red blood cells should be allowed to be transfused.

Incidentally, the elevated prothrombin time may be explained by the intravascular hemolysis, for the red cell stroma is a good source of thromboplastin.

DR. BLOUNT: What would be the symptomatic management of an episode of acquired acute hemolytic anemia due to autoimmune states?

DR. FANCY:** The treatment of hemolytic anemia is first to locate and remove the cause. Often this is not possible. Blood transfusion may occasionally be required; however, the presence of panagglutinins may make cross matching difficult and transfusion reactions frequent. When transfusions are necessary, packed red cells or saline-washed red cells should be used.

Corticotropin and adrenal steroid therapy has been a great advance in the treatment of hemolytic crises. Antibodies cannot always be demonstrated by present tests so that these agents are always worth a trial in acquired acute hemolytic anemia. In the presence of a positive Coombs test, steroids are almost always beneficial. Suggested dosages are: corticotropin, 25–50 USP units intramuscularly every 6 hours;

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*Capt. George C. Hewitt, MC, USA, hematologist.
**Lt. Col. Henry F. Fancy, MC, USA, resident in medicine.

Figure 1. Cut surface of liver, showing numerous gas bubbles.

cortisone, up to 300 mg daily; prednisone, 100 mg daily. When a response is observed, the dose is reduced, although a maintenance dose is occasionally necessary to prevent hemolysis. The therapy in this case, as it was started, appears adequate.

DR. BLOUNT: Not all hemolytic crises are due to antibodies. Blackwater fever, sickle cell anemia, and paroxysmal nocturnal hemoglobinuria are examples of diseases in which spontaneous hemolytic crises develop in the absence of any autoimmune mechanism. A septic abortion associated with fulminating infection due to *Clostridium welchii* has in my own experience, both here and in Europe, caused devastating hemolysis such as occurred in this case. In another instance an acute hemolytic state associated with fatal anuria was seen at this hospital following the use of an abortifacient paste.

DR. TESCHAN: One problem which can arise is ingestion of the wrong pills. A recent report tells of a laboratory instructor who ingested sodium chlorate instead of sodium chloride. A massive hemolysis resulted, with renal shutdown. Aggressive therapy, including repeated dialyses with an artificial kidney, brought him through alive.

DR. BLOUNT: In summary, this patient had a fulminating hemolytic process leading to death within 3 days. The immediate cause of death was probably a thrombotic episode, since thromboses are so apt to occur in the various hemolytic disorders. The most likely explanation

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for this entire process, and the diagnosis I prefer, is septic abortion, probably due to *Clostridium welchii*. The patient probably also had a drug-induced methemoglobinemia. Since the clinical and laboratory data available do not provide conclusive evidence of the above states, I must also mention the possibility of the presence of some chronic hemolytic disorder, with an aregenerative crisis. A third and distinctly possible explanation would be chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria.

DR. BLOUNT'S DIAGNOSES:

1. Septic abortion, with *Clostridium welchii* septicemia
2. Methemoglobinemia, drug induced

PATHOLOGIC FINDINGS

DR. KIEL:* At autopsy the body still showed its peculiar discoloration, having a distinct brown hue, especially on the face and hands;

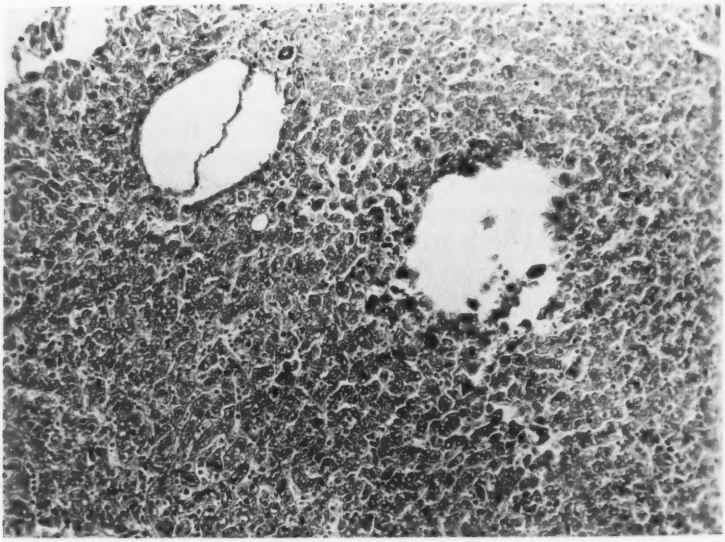

Figure 2. Photomicrograph of liver, showing gas bubbles lacking inflammatory reaction. (x 105)

*Capt. Frank W. Kiel, MC, USA, resident in pathology.

darker still were the lips and nailbeds, which were purplish. When the internal organs were exposed, an advanced state of decomposition was detected, despite continuous refrigeration of the body during the 20 hours following death. The retroperitoneal tissues were foamy in character, containing clear gas bubbles up to 5 cm in diameter.

Figure 3. ***Clostridium perfringens*** **bacteria in liver. (x 1350)**

The liver surface was marred by numerous small gas bubbles beneath the capsule; the cut surface was riddled by cystic cavities of varying size, presenting a honeycomb appearance (fig. 1). Microscopically, the cavities seemed innocuous, for there was no inflammatory reaction associated with them (fig. 2). However, scattered among them and throughout the hepatic parenchyma were plump rod-shaped bacteria, in chains and singly, identified as clostridium organisms (fig. 3).

The kidneys were softened and blackened, with indistinct cortical markings. Many hemoglobin and red cell casts were seen microscopically, along with acute congestion, indicating an early hemoglobinuric nephrosis.

Figure 4. Enlarged uterus, showing shaggy endometrium.

Enlargement of the uterus was noted; it measured 10 cm in height. The cervical os was gaping, and the endometrial wall was shaggy, as if recently scraped (fig. 4). In the dark crumbly blood clot in the uterine cavity were found chorionic villi on microscopic examination, indicating a recent pregnancy (fig. 5).

Cultures of the heart, liver, and spleen yielded *Clostridium perfringens* in profusion.

This organism, formerly called *Clostridium welchii*, still is a major cause of death in postabortal infections, mostly after attempts at induced abortion. The alpha toxin which the organism elaborates is responsible for the massive hemolysis; it is a lecithinase which acts on lecithin complexes on the surface of the red cell, producing hydrolysis of the lecithin with rupture of the cell membrane.[4] Other toxins are produced also, including a necrotizing toxin (causing skin necrosis), a myotoxin (causing spasmodic twitching), a neurotoxin, and a nephrotoxin. If the hemolytic episode is survived, the patient often develops acute renal failure, usually irreversible, but from which a few women have recovered.[5]

The course of the disease is usually inexorably progressive. If the organism is introduced into a uterus containing dead fetal tissue, incubation will occur and an endometritis develop in 24 to 48 hours,

Figure 5. Chorionic villi found in material within uterine cavity. (x 170)

proceeding to physometra—the gas-filled uterus. Spread to adjacent pelvic and peritoneal tissues occurs secondarily. Through the placental site, blood stream infection is easily accomplished, leading to bacteremia, septicemia, and metastatic gas gangrene.

Thus, the young woman in this case succumbed to postabortal *Clostridium welchii* septicemia. Although the criminal case is not yet solved, the probable sequence of events is as follows: The routine physical examination that she had was probably one which confirmed the fact that she was pregnant. Her activities are unaccounted for during several hours after this examination; an abortion was presumably induced during this time. Symptoms first developed 48 hours later, when she became weak while at work. The fulminating terminal events occurred 2 days later, on the fourth day postabortion. Pelvic disease was not considered in the diagnosis during life, largely because of the patient's minimal pelvic manifestations. The minimization of abdominal complaints may have been due partly to difficulty in communication (she was of Latin-American background) or more likely to deliberate concealment.

PATHOLOGIC DIAGNOSES:

1. *Clostridium perfringens* (*welchii*) septicemia with massive hemolysis
2. Acute endometritis, secondary to induced abortion
3. Hemoglobinuric nephrosis, early

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NEW NAME FOR OLD SPECIALTY

The protracted betrothal of gynecology to obstetrics has culminated in a union that now appears so firm as to no longer justify retention of the maiden name or the cumbersome composite of both. . . . Is it not time, therefore, that we take the last, logical step in recognition of our specialty's unit, and modernize its terminology? . . . *Gyniatrics* (from the Greek *gyné*, meaning woman; and *iatros*, physician or medicine; *iatrikos*, healing; *iatriké*, treatment of disease) suggests itself as a modern English language replacement for the honorable but tired double name obstetrics and gynecology (cf. pediatrics, geriatrics); and *gyniatrician* for the combined obstetrician-gynecologist. Obstetrics and gynecology have been joined in fact. Does not this union merit a proper name?—HAROLD SPEERT: A New Name for Our Specialty? *American Journal of Obstetrics and Gynecology*, July 1959.

Case for Diagnosis

MAJOR EDWARD H. JOHNSTON, MC, USA

A 61-year-old white male veteran was found unconscious, rigid, and cyanotic, face down on the dining-room floor. An orderly stated that the patient had had similar seizures on previous occasions on the ward. In spite of artificial respiration, the patient was pronounced dead by a physician 15 minutes later. Since no cause of death was apparent, the case was referred to the medical examiner.

Diagnosis?

Please turn the page.

From the Armed Forces Institute of Pathology. This month's Case for Diagnosi is AFIP Accession No. 866179, contributed by the Veterans Administration Hospital, Northport, L.I., N. Y.

Diagnosis and Discussion

Postmortem examination revealed a large fragment of partially chewed beef impacted in the proximal portion of the esophagus. This mass depressed the epiglottis over the lumen of the larynx, thereby preventing air passage.

Two important points can be learned from this case:

(1) Obstruction of the airway must be considered when anyone is found cyanotic, with or without convulsions, in a dining room or eating establishment.

(2) Examination of the neck organs must be included at autopsy, since, as in this case, the cause of death might otherwise be missed.

Reference. Gonzales, T. A., Vance, M., Helpern, M. and Umberger, C. J.: *Legal Medicine*, ed. 2, Appleton-Century-Crofts, Inc., New York, N.Y., 1954, pp. 480–482.

Rapid Identification of *Neisseria meningitidis* by Fluorescent Antibody Technic

MAJOR JOSEPH F. METZGER, MC, USA
MAJOR CHAUNCEY W. SMITH, USAF, MSC

SINCE THE INTRODUCTION of the fluorescent antibody technic,[1] great strides have been made not only in its application but in its simplification. Its use in the clinical laboratory is now justified, provided suitable controls are employed and technical difficulties inherent in the technic are completely understood. The literature describes methods for the detection of *Malleomyces pseudomallei*,[2] *Pasteurella pestis*,[3–5] streptococci,[6, 7] *Shigella flexneri*,[8] staphylococci,[9] *Erysipelothrix insidiosa*,[10] *Listeria monocytogenes*,[11] yeasts and fungi,[12, 13] the organisms of influenza,[14] herpes simplex,[15] and rabies,[16] and cholera vibrios.[17] Application of these methods is restricted because of the limited availability of immune sera at the present time. The feasibility of utilizing readily available antisera for rapid identification was investigated, using *Neisseria meningitidis* as the test organism.

MATERIALS AND METHODS

Antisera, representing the 4 serologic groups of *N. meningitidis* [18] and 2 polyvalent antisera, were conjugated with fluorescein isothiocyanate.[19] Bovine serum albumin conjugated with lissamine rhodamine RB 200 was added as a counterstain,[20] combining 1 volume of the lissamine-conjugated serum to 20 volumes of the fluorescein-labeled serum. Pooled normal rabbit serum and *Erysipelothrix insidiosa* and *Listeria monocytogenes* antisera were used as controls. The control sera were conjugated with fluorescein isothiocyanate and the counterstain added in the manner previously described.

The meningococci were maintained in NIH semisolid medium

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(BBL) and prior to testing were streaked on heart infusion blood agar. The remaining test organisms were grown and maintained as generally prescribed. Suspensions of bacteria, grown at 37°C for 18 hours, were made in saline and 10 percent formalin. These suspensions were placed on clean slides, dried in air, and fixed by heat. The smears were overlaid with conjugated sera, placed in a moist chamber at 37°C for 30 minutes, washed in buffered saline (pH 7.2) for 10 minutes, and mounted in glycerol buffered to pH 7.2. Duplicate slides were stained with the pooled normal serum and the *Listeria* and *Erysipelothrix* antisera.

An American Optical "Pathostar" microscope, with a dark field condenser, an American Optical Merc-Arc illuminator, a riboflavin (B_2) exciter (Corning 5113), and riboflavin (B_1) barrier filters (Corning 587), were used to demonstrate fluorescence.

RESULTS

The *N. meningitidis* immune sera were tested against 16 strains of *N. meningitidis* representing the 4 serologic groups Individual cells fluoresced brightly following treatment with their group-specific immune sera, in both saline- and formalin-prepared smears. The polyvalent sera produced fluorescence in all strains. Cross reactions were observed between the various strains of *N. meningitidis* when the group-specific sera were used. When normal control serum and immune *Listeria* and *Erysipelothrix* sera were applied, there was no reaction.

All sera were tested against the following species (figures in parentheses indicate number of strains tested): *Neisseria catarrhalis* (4); *N. flavescens* (3); *N. gonorrhoeae* (8); *N. haemolysans* (1); *N. perflava* (2); *N. sicca* (1); *N. subflava* (1); *Diplococcus pneumoniae* (4); *Streptococcus pyogenes*, groups A–G; *Listeria monocytogenes* (30); *Mimae* sp. (12); *Herellea* sp. (15); *Bacillus anitratum* (6); *Erysipelothrix insidiosa* (25); *Staphylococcus pyogenes*, types I–VIII. One strain of *N. gonorrhoeae*, a recent isolate, produced slight fluorescence. The remaining strains did not fluoresce but presented an orange-red color, indicating a nonspecific reaction.[20]

COMMENT

Rapid identification of *N. meningitidis* is important for selection of the proper therapy. Usually, the tentative laboratory diagnosis is based on morphology and on the reaction to Gram's stain and is later confirmed by cultural methods. The conjugated polyvalent meningococcus antiserum provides a rapid, specific means of identification.

With the group serum, however, there were some cross reactions between groups, and organisms could not be serologically separated. Undoubtedly, with absorption technics this crossing could be eliminated for use in epidemiologic studies. On the basis of these results, it would seem feasible for the clinical laboratory to employ other commercially available sera to facilitate the diagnosis of acute disease entities, such as infections with *Haemophilus influenzae* and *Diplococcus pneumoniae*, both in pure culture and in clinical specimens such as spinal fluids. It is now possible for the clinical laboratory to participate in clinical evaluations by means of this technic, especially with reasonably priced ultraviolet light sources available for use with a standard microscope and a dark field condenser.

It cannot be overemphasized that any serum employed must be fully characterized, not only against a panel of related agents, but also against any so-called "nonpathogens" that could possibly be present in the specimen. As stated by Smith and his associates,[11] there is insufficient information concerning minor cross reactions between bacterial, viral, and mycotic agents, formerly considered unimportant but detectable by this technic. These investigators also pointed out that so-called "normal" serum must no longer be considered normal but must be characterized along with the immune serum. In contrast to the serologic antisera available, which are not sensitive enough to permit detection of intrinsic antibodies, this technic makes it possible to detect 1 organism per microscopic field—a degree of sensitivity that has implications previously considered unimportant in serologic procedures.

Carter and Leise recommended [21] that a single fluorescein-labeled antispecies globulin be used with the indirect technic,[22] eliminating the necessity of preparing a labeled antiserum for each organism studied. These authors failed to point out, however, that the antispecies globulin would also contain acquired antibodies that could cause specific reactions. In 1949, using the complement-fixation test, Reyn [23] found that only 30 percent of 1,000 rabbits screened did not give a gono-reaction; this reaction was caused by antigens shared in common by certain pasteurella strains and gonococci. It would therefore be desirable to characterize this antispecies globulin. Since the conjugation technic has been simplified so that it requires no specialized equipment and can be performed in the small laboratory, it would seem more feasible to conjugate individual sera, thus eliminating another indeterminate factor.

Care should be taken to control pH and tonicity in order to avoid diminishing or quenching specific fluorescence. The pH of the glyc-

erol mounting medium is of great importance: if only slightly within the acid range, fluorescence will be quenched.

Heretofore it has been difficult to detect infectious agents in samples containing protein material, such as impression smears and formalin-fixed tissues, because the nonspecific uptake of fluorescein-labeled material in substances that do not show definite morphologic characteristics made it difficult to localize specific fluorescence. This difficulty is increased by the fact that oil immersion is not ordinarily employed with this technic because of the low intensity of ultraviolet fluorescence. The use of the counterstain,[20] however, generally eliminates nonspecific uptake, so that diagnosis based on this technic becomes possible.

SUMMARY

A method for rapid identification of *Neisseria meningitidis* by the fluorescent antibody technic, using a polyvalent serum, is presented. Cross reactions with 20 strains of related *Neisseria* species were negative, with the exception of a slight cross with one strain of *Neisseria gonorrhoeae*. Specific staining was not obtained with 107 other organisms tested. The use of this technic in the clinical laboratory is discussed.

ACKNOWLEDGMENT: Appreciation is expressed to Dr. Arthur Abrams, chief, Diagnostic Reagents Section, Walter Reed Army Institute of Research, and Dr. Michael F. Barille, Division of Biological Standards, National Institutes of Health, for their generous supply of antiserum.

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Case Reports

Meningococcemia: A Cause of Prolonged Fever

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MENINGOCOCCEMIA is usually a brief and early phase of meningitis, but it may be prolonged and unaccompanied by any signs of meningeal inflammation. Subacute or chronic meningococcemia is rarely seen, except when troops are mobilized. Carbonell and Campbell [1] collected 30 cases from the American literature prior to 1938 and reported on 3 of their own, seen between 1929 and 1937. Heinle [2] noted 5 cases between 1929 and 1936 at a Cleveland hospital.

The paucity of reports since the discovery of the sulfonamides and antibiotics suggests that the incidence or recognition of prolonged meningococcemia has dropped even lower. The experienced internist, who rightly withholds chemotherapy until he has an etiologic basis for its use, is more likely to encounter prolonged meningococcemia than is the novice, who, administering penicillin indiscriminately for unexplained fevers, cures the disease in its early stages. Thus, since the diagnosis can easily be delayed indefinitely or be completely missed, early recognition is a matter of considerable importance.

The purpose of this article is to present a case of prolonged meningococcemia without meningitis and to offer diagnostic clues that help differentiate this entity from other diseases causing prolonged fever.

CASE REPORT

The patient, a 22-year-old soldier, experienced malaise, moderate headache, fever, and generalized moderate myalgia on 7 April 1959. He was seen in a dispensary where, despite absence of an epidemic, influenza was suspected. Aspirin was

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prescribed and his condition improved. On 15 April, the symptoms returned and he noticed a rash. He was hospitalized on 16 April.

Physical examination disclosed many "erythematous macules" and "maculopapules" on the patient's arms and legs, temperature of 101.6° F, pulse rate of 110 per minute, and mild conjunctivitis. White blood cell count was 8,800 per cu mm, with 88 percent neutrophiles. The patient received salicylates, and in 12 hours his temperature became normal and remained so. He was discharged 36 hours after admission, feeling well. The rash was still present but it had begun to fade.

Malaise, fever, and rash recurred on 21 April, and the patient's ankles became red, swollen, and painful. The rash persisted. On 27 April (20 days after onset of symptoms), the patient was readmitted to this hospital after experiencing a chill the night before.

On this admission the patient's temperature was 101° F, and his pulse rate 84. Leukocytosis of 14,900, with polymorphonucleocytosis of 85 percent, and a corrected sedimentation rate of 34 were present. Culture of pharyngeal secretions disclosed *Neisseria catarrhalis* and alpha hemolytic streptococci. Urine culture was sterile. There were no meningeal signs or other abnormalities except for moderate tenderness of the joints of all extremities and a rash consisting of round pink and red macules and maculopapules, which blanched when pressed. Most of the lesions measured 1 mm in diameter, although some were 4 to 5 mm. Many were upon tender, raised, slightly inflamed areas, occurring in clusters over the extensor surfaces of all extremities and over the buttocks. After 2 days, small purple centers were visible in a few lesions and by 5 May many lesions were purple.

Despite administration of 90 grains of aspirin every day, temperature peaks of 101° F to 102° F occurred daily until 9 May, when the patient's temperature ascended to 104° F and his pulse rate (which had been 80 to 90 per minute) rose to 126. Biopsy of a skin lesion, performed on 6 May, revealed inflammatory infiltrate about several minute vessels. Granulocytes were scarce. The lesion was considered consistent with inflammatory purpura, and a microscopic diagnosis of "vasculitis" was made. Because of our diagnosis of acute vasculitis or Schönlein-Henoch purpura, dexamethasone, 9 mg per day, was begun on 10 May. The patient's temperature and pulse dropped to normal within 24 hours and remained so for the rest of his hospitalization, and his other symptoms rapidly disappeared. No new skin lesions appeared, and in a week all lesions were gone.

On 12 May, 2 days after initiation of corticosteroid treatment and dramatic improvement, however, the laboratory reported that all 3 blood cultures (drawn on 4 and 5 May) revealed *Neisseria meningitidis*. Two other samples of blood, drawn as soon as the report was received, also yielded *N. meningitidis*. Spinal fluid examination revealed normal pressure, no cells, and normal glucose and protein values. Smears and culture of fluid gave negative results. The patient received 3 million units of penicillin intravenously, followed thereafter by intramuscular injections of 1.2 million units daily from 13 to 21 May, and 0.6 million units daily from 22 to 26 May. The dosage of dexamethasone was gradually reduced to 0.75 mg per day by 23 May, and the steroid was discontinued 25 May. All cultures of blood drawn during and after penicillin therapy—2 specimens each on 15, 20, 22, 28, and 29 May—were sterile.

Roentgenograms disclosed increase of heart diameter on 27 April (compared with 17 April) and return to normal on 4 May. Electrocardiograms on 28 and 30 April were normal, but a tracing on 4 May revealed an increased P–R interval

(0.26 seconds), present in this tracing only. A tracing on 11 May showed barely erect T waves in V_5 and R : T ratio of 30 : 1 in V_4. Electrocardiograms thereafter (on 14, 18, and 21 May) were normal.

Blood cell count and sedimentation rate were normal on 1 June.

DISCUSSION

Subacute or chronic meningococcemia, without meningitis, can persist for weeks or months—and probably for over a year. In the first such case, reported by Salomon [3] in 1902, the patient had bacteremia and a fever for 2 months before meningitis developed. One of Heinle's [2] patients was ill for 5 months and one, he believed, had had meningococcemia for years. In this antibiotic era, such long periods of fever will probably never occur in the United States.

The diagnostic features of chronic meningococcemia are prolonged fever, rash, joint pains (often objective joint abnormalities), and marked leukocytosis and polynucleosis.

Several diseases characterized by a rash and several characterized only by prolonged fever should be considered in the differential diagnosis. Only the most important points of differentiation will be emphasized here.

Acute vasculitis (allergic angiitis, Schönlein-Henoch purpura) is the disease most likely to cause difficulty in the present era. When the senior author and a consultant first saw this patient, they considered the rash characteristic of Schönlein-Henoch purpura—not only because of the size and distribution of the lesions, but also because of their appearance and evolution.

The rash of chronic meningococcemia is practically identical with that of Schönlein-Henoch purpura. In both conditions pink and red macules and papules occur, often on tender and indurated areas, in groups and recurrent crops, with a predilection for extremities. Lesions soon show petechial or purpuric centers. Unlike some other prolonged fevers in which skin lesions are important, individual lesions are not chronic but disappear, only to be succeeded by repeated crops.

The absence of erythrocytes in the urine militated against acute vasculitis, but not strongly so. Absence of overt physical signs of arthritis decreased the probability of Schönlein-Henoch purpura. If arthritis had been present, however, it would not have been a strong feature in favor of Schönlein-Henoch purpura because patients with chronic meningococcemia often have acute arthritis.

The distinction between subacute or chronic meningococcemia and Schönlein-Henoch purpura may be almost impossible on clinical grounds—and even, as illustrated in this case, by histologic criteria—unless the purpuric spots become much larger. Therefore, if leukocy-

tosis and polynucleosis are discovered in a patient believed to have acute vasculitis, blood cultures and stained smears of the skin lesions must be obtained if meningococcemia is to be excluded.

Patients with typhoid, typhus, trichinosis, systemic lupus, dermatomyositis, and subacute bacterial endocarditis may all have skin lesions, which, however, differ in appearance, distribution, evolution, and duration from lesions seen in meningococcemia. There are many other differences: for example, patients with typhoid or trichinosis have gastrointestinal symptoms; typhus is a brief disease; in systemic lupus and dermatomyositis many organs are usually involved. A diagnosis of subacute bacterial endocarditis does not exclude chronic meningococcemia because acute or subacute endocarditis may be due to meningococcic septicemia. Etiologic diagnosis must depend on results of blood cultures.

The rash distinguishes meningococcemia from all the diseases mentioned except acute vasculitis. Although the rash is rarely absent, a few patients with meningococcemia with no skin lesions have been described (one of the 5 reported by Heinle [2]; 3 of 36 mentioned by Carbonell and Campbell [1]). Thus, absence of a rash does not eliminate the possibility of meningococcemia, but it renders the diagnosis impossible without laboratory study and identification of the organism in the blood.

Among the diseases with prolonged fever, but usually without rash, that may be simulated by meningococcemia are rheumatic fever and brucellosis. Rheumatic fever and meningococcemia are often preceded by sore throat; and pericarditis, myocarditis, or endocarditis can occur in both diseases. Adult rheumatic fever patients usually have more obvious arthritis; fever is favorably affected by salicylates. Pronounced leukocytosis and polymorphonucleosis should cast doubt on the probability of rheumatic fever. Brucellosis and chronic meningococcemia without a rash could resemble each other clinically, but polymorphonucleocytosis points to the latter. Results of blood cultures will, of course, be decisive.

A third group of diseases must be mentioned because some patients with meningococcemia (without meningitis) have sought medical attention for symptoms characteristic of acute or subacute endocarditis, myocarditis, or pericarditis, suppurative sinusitis, arthritis, or pleuritis.[4] Therefore, meningococcemia must be remembered as a cause of any of these pathologic entities.

With increasing emphasis on diseases of autoimmunity, we are inclined to think first of a collagen disease when patients are febrile for more than a month. Therefore, this case report may serve as a useful reminder that prolonged fever can be caused by bacteria.

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SUMMARY

Meningococcemia may exist without signs of meningeal inflammation and may be prolonged. Chronic meningococcemia is infrequently recognized, particularly since the advent of sulfonamides and antibiotics. A case of prolonged meningococcemia without meningitis is presented. The patient showed dramatic clinical response to dexamethasone, administered because allergic vasculitis was suspected, and there was prompt bacteriologic response to penicillin, administered when blood cultures were reported as positive for *Neisseria meningitidis*. The differential diagnosis between chronic meningococcemia and other diseases causing prolonged fever or rash or both is discussed. In particular, the rash can often not be distinguished clinically or histologically from that of Schönlein-Henoch purpura; and if it is absent, the diagnosis is impossible without identification of the organism in blood cultures.

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A Shipboard Eye Hazard

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PENETRATING EYE INJURIES, no matter how small, should never be considered trivial. They are emergencies demanding immediate attention. The most common injuries resulting from industrial hazards are caused by flying particles, and it is estimated that 20 percent of all cases of uniocular blindness are due to these occupational injuries.[1]

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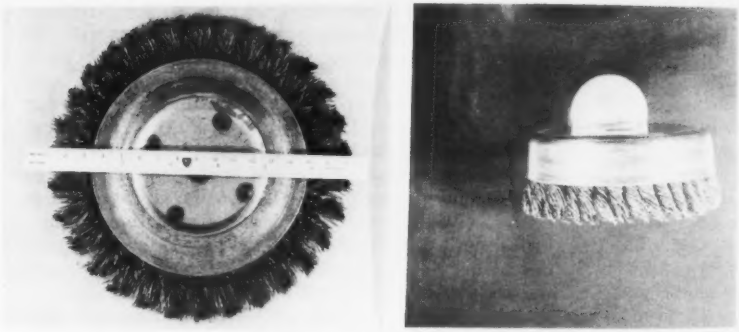

Figure 1. Disk (left) and cup (right) types of power-driven wire brushes.

Aboard ship, especially during shipyard maintenance and repair, power-driven wire brushes or buffers are used extensively in abrasive work. Commonly used disk and cup types of wire brushes are illustrated in figure 1. The individual wires are about 2.5 cm long and of substantial caliber. When in motion the wires may break off, becoming flying particles and an ocular hazard, as illustrated by the following case report.

CASE REPORT

A 20-year-old white seaman was injured on 18 November 1959 while using a wire buffer for "paint chipping" in the galley aboard ship. He experienced a "bright flash of light and then no vision" in his left eye.

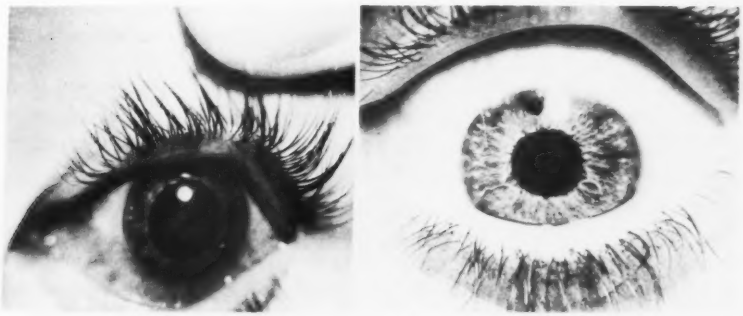

Figure 2 (left). Traumatic cataract, OS, following penetrating wire injury.
Figure 3 (right). Appearance of eye following linear extraction of lens, with the VOS correctable to 20/20.

On admission, the VOD was 20/20 and VOS, light perception only. A penetrating tract with "rust" deposits was present in the inferonasal quadrant of the left cornea. The anterior chamber was deep; with a 4+ cell and flare. Through a rent in the anterior lens capsule a small amount of cortex protruded into the anterior chamber. The left eye was hypotonic and the fundus could not be visualized through the opaque lens (fig. 2). Orbital roentgenograms failed to reveal the presence of a metallic intraocular foreign body.

Treatment consisted of atropinization of the left pupil, binocular eye pads, tetanus booster, and systemic chemotherapy. Twelve days following injury, acute glaucoma developed, with the intraocular tension greater than 75 mm Hg Schiøz. This did not respond to intravenous and oral Diamox (acetazolamide), and emergency linear extraction of the left lens was performed. The operation was uncomplicated and the patient's postoperative course was uneventful.

Three months after injury the left eye was quiet and asymptomatic (fig. 3). The patient was fitted with a monocular aphakic contact lens, which corrected the VOS to 20/20 and was well tolerated; fusion was present.

DISCUSSION

Flying particles have produced minor injuries of the lid and abrasions and lacerations of the cornea and conjunctiva, including such major injuries as the one described in this case report. In our opinion, the blink reflex protects the subject in many instances and usually dislodges the wire particle from the eye. This must have occurred in the case reported, since orbital roentgenograms failed to reveal the presence of a metallic foreign body, and clinically the patient showed no signs of developing siderosis bulbi. We have treated one patient who pulled the wire from his cornea when it was trapped between the lids. However, it must be stressed that the wire, or a fragment of it, may be retained as an intraocular metallic foreign body. This should always be considered a possibility; roentgenograms should be taken, and when available the Berman locator should be utilized. Following lens extraction, the lens material should be carefully examined for the presence of a foreign body.

Since blindness can result from penetrating ocular injuries, it is urged that proper shielding devices always be used on all types of power-driven brushes and that personnel operating this equipment be provided with adequate protective devices for their eyes.

SUMMARY

A case of a penetrating ocular injury caused by a flying particle from a power-driven wire abrasive brush is reported. Twelve days following injury, the patient developed acute glaucoma in the injured eye, which failed to respond to conservative treatment. Emergency linear

extraction of the lens was performed. Three months after the injury, vision was corrected to 20/20 with a monocular aphakic contact lens. This type of abrasive wire brush, commonly used aboard ship and at Navy yards, is discussed as an ocular hazard, and it is urged that proper shielding and protective eye devices be provided for personnel operating this equipment.

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Nonunion of Avulsion Fracture of Tibial Intercondylar Eminence

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IT IS THE PURPOSE of this article to report a case of nonunited avulsion fracture of the tibial intercondylar eminence treated unsuccessfully by conservative means and cured by open reduction with reduction of the fracture 10 months after injury.

Fracture of the intercondylar eminence was first described by Poncet[1] and Dittel[2] in the latter part of the nineteenth century. Blaisdell[3] carried out a series of experiments on cadavers, in which he demonstrated that force applied in the direction to cause rupture of the anterior cruciate ligament would cause avulsion of the intercondylar eminence. The injury is usually produced by anterior displacement of the tibia on the femur as well as by excessive internal rotation of the tibia upon the femur to cause avulsion of the tibial spines.[4, 5] Lang[6] called these fractures crucial ligament fractures.

Most textbooks recommend immobilization of the lower extremity for 6 weeks as adequate conservative therapy for undisplaced avulsion fractures of the intercondylar eminence of the tibia.[7–9] Some recommend rotation maneuvers to replace displaced fractures that block extension of the knee, followed by cast immobilization.[10] Roth[11] be-

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lieves that the lateral meniscus is often displaced in such a way that it folds under the bony fragment and obstructs reduction. Others have not found manipulative reduction successful and recommend open reduction by arthrotomy of the knee with fixation of the displaced fragment into the defect in the tibia.[5] Lee[12] recommends repair by wire sutures for this injury when the bone fragment is displaced. MacAusland[13] advocates open reduction and fixation of the fragment by a Vitallium screw after reduction. Jones and Smith[14] advocate surgical excision of the bony fragment if it blocks full extension.

If these fractures are not recognized and reduced, persistent limitation of extension of the knee will result. Böhler[15] emphasizes this and the need for early reduction. Fractures of the tibial spine, older than 10 days, will usually not be replaced by manipulation because the bed has been filled with blood clots, fibrous tissue, or callus. These cases require open reduction.

Meyers and McKeever[5] present an excellent study of 45 cases, 10 of which were in adults. They classify the injuries into 3 types: (1) cases with no displacement of the fragment from the bed of origin, (2) partial dislodgment of the fragment but good apposition of a large portion of the fragment, and (3) complete dislodgment of the avulsed fragment from its bed with no bone apposition of the fragment. They recommend conservative treatment for types 1 and 2, and open reduction followed by immobilization for type 3 injuries. In none of their cases could a displaced fragment be replaced by manipulation.

Böhler[15] reports a case of nonunion of fracture of the tibial spine with surgical removal of the bone fragment 7 months after injury. He considers it better to deepen the tibial bed from which the piece was avulsed and to fix it in place. This would prevent some anteroposterior instability found as a residual disability. Many textbooks advocate removal of the bony fragment in old cases.[8] Meyers and McKeever[5] describe 1 case treated 11 years after injury because of the presence of a loose body and persistent catching of the knee. The fragment could not be replaced and was excised. In another case a child was treated surgically 5 months after injury, with replacement of the displaced bone fragment by chromic sutures, plus immobilization, with good results. In a case of nonunion Meyerding and Walsh[16] used fixation with a beef-bone screw. The initial injury had occurred 6 years before surgical repair, and a good result was obtained. In 2 cases Venable[17] excised the fragments.

No additional case reports on nonunion of avulsion fractures of the intercondylar eminence of the tibia have been found on review of the literature available. Very little emphasis is placed on this

entity as a cause of disabling symptoms and internal derangement of the knee. Bradford, Adams and Magill [18] emphasized the difficulty in diagnosis of these lesions compared with other causes of internal derangement. Though roentgenography will reveal the bony injury, caution in excluding meniscus injuries must be observed. This disability and the difficult differential diagnosis were present in the following case.

CASE REPORT

A 33-year-old white man first injured his knee on 22 May 1956. He was treated for avulsion fracture of the anterior tibial spine by cast immobilization for 6 weeks in another hospital. This was followed by ambulation with crutches and a prolonged period of physiotherapy. He had been returned to light duty in the military service on 22 October and had unsuccessfully made an effort to resume normal activities.

On January 1957 the patient was admitted to this hospital, complaining of pain and swelling of the right knee. He stated that the knee had remained painful since he had resumed ambulation following the injury in 1956. The knee had never locked, but the patient complained of a clicking sensation in his knee at times and pain with each step.

Examination showed that the patient walked with a stiff-legged gait on the right, with the knee flexed 15°. He claimed that he suffered pain in walking with a normal swinging-knee gait, and he performed this poorly. There was pain to palpation over the anteromedial joint line, and on flexion a thin painful rim of tissue was palpable over the medial joint line. Flexion was limited to 95°. Attempts to complete flexion and extension of the knee were accompanied

Figure 1. Anteroposterior and lateral roentgenograms of knee showing nonunion of avulsion fracture of intercondylar eminence.

Figure 2. Postoperative roentgenogram of knee. Fracture has been reduced and appears united.

by pain. The lateral ligament was stable. The medial collateral ligament exhibited slight laxity, and the anterior cruciate ligament moderate laxity. McMurray's test was positive, with pain and a definite cartilage click felt on some examinations of the knee.

Roentgenograms of the right knee revealed an irregular loose bony fragment in the mid-anterior aspect of the knee joint. A defect in the region of the anterior tibial spine suggested that previous fracture was the origin of this bony fragment (fig. 1).

The patient received physiotherapy to regain strength of the quadriceps musculature. Below-knee skin traction was applied to restore extension of the knee. The knee slowly straightened and the patient improved on physiotherapy.

Full knee extension was possible with more than 30 pounds of resistance by 1 March. In spite of this improvement the patient still suffered pain on walking with a normal gait and preferred to walk with leg stiff.

On 20 March an arthrotomy of the knee was performed. The medial meniscus was excised because of the diagnosis of tear. No true tear was discovered. Inspection of the knee upon testing of the anterior cruciate ligament showed abnormal anteroposterior mobility due to a loose nonunion of the fracture of the intercondylar eminence. The ligament was intact, but the loose bony fragment moved with an excursion of ⅜ to ½ inch upon tests performed at the time of operation. The bony fragment was exposed and freshened by sharp dissection and bone curettage. The tibial bed from which the tibial spine fracture had been avulsed was deepened and freshened with a curet. The anterior surface of the tibia was exposed. Drill holes were placed through the anterior tibial cortex into the prepared defect. A wire suture was passed through a drill hole, across the fragment through the cruciate ligament, and emerged through the second hole to the outer tibial cortex. When this wire was made tight, it pulled the ununited fragment into the prepared bed in the tibia. It was made fast by tying over the outer tibia after the method of Lee.[12] The stability of the knee was found to be restored when tested. The wound was closed and the knee immobilized in a cast at 165°.

The limb was immobilized for 6 weeks. Active motion was then begun and the patient improved rapidly with physiotherapy. He had resumed a normal pain-free gait by 21 June. One month later the patient's knee was asymptomatic, his gait was good, and he was returned to a full-duty status. He was performing arduous physical activity with few complaints when rechecked 5 months after the surgical intervention. Bony union had been obtained at the site of nonunion (fig. 2).

SUMMARY

A case of fracture of the intercondylar eminence of the tibia that resulted in nonunion is reported. This was treated successfully by reduction of the fracture 10 months after injury.

Failure of fractures of the intercondylar eminence to unite produces limitation of knee extension and disability. The disability is at times difficult to differentiate from internal derangement produced by meniscus injuries.

Completely displaced fractures of the intercondylar eminence should be treated early by open reduction and internal fixation to avoid prolonged disability. For best results, such fractures should be repaired by reduction of the ununited bony fragment, if possible, rather than by excision.

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Chronic Melioidosis: Serologic Diagnosis and Antibiotic Treatment

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MELIOIDOSIS is a specific glanders-like infection in human beings first described in 1912 by Whitmore and Krishnaswami,[1] who discovered the disease while performing postmortem studies on Rangoon beggars. A total of some 300 cases of melioidosis are recorded in the world literature. Approximately two thirds of these cases occurred in the Rangoon, Burma, area. Melioidosis has also been reported as occurring in Malaya, Indochina, Ceylon, Thailand, Indonesia, Singapore, southeast China, and Guam.[2,3] The first case from the Western Hemisphere was reported by McDowell and Varney[4] in 1947. A total of 4 cases have been reported in patients from this geographic area, only 2 of them in persons who had never left the United States.[5–7] In 1957, Prevatt and Hunt[6] summarized the reported cases of chronic melioidosis and found that all patients except 1 were males. All but 1 case occurred in adults.

It is believed that melioidosis is primarily a disease of rodents, but cats, dogs, and monkeys are easily infected, whereas horses are apparently relatively insusceptible.[8] Dissemination is usually by contamination of food or water with rat excreta; however, experimental transmission of the disease by the *Aëdes aegypti* mosquito[9] and the rat flea (*Xenopsylla cheopsis*)[10] has been demonstrated. Susceptible animals may be infected by oral, parenteral, or intraperitoneal routes, as well as by contamination of the abraded skin with the causative organism, *Malleomyces pseudomallei*. Melioidosis is thus rather common among narcotic addicts, but man-to-man transmission has never been reported.[6]

Acute melioidosis is usually manifested by a pulmonary infection of sudden onset, with moderate to high fever, followed by hematogenous dissemination of the causative organism and widespread visceral involvement, prostration, and death in a few days. However, the chronic form resembles tuberculosis or a mycotic infection, with a more gradual onset and evidence of multiple small discrete abscesses of the skin and viscera, which may become confluent and form

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sinuses.[7] Although chronic melioidosis usually develops in patients who have survived the acute phase, it may occur without previous manifestations of acute illness. The chronic form is commonly found in Europeans, whereas the acute form is seen more often in the Far Eastern population.[11]

The causative organism is usually classified as *Malleomyces pseudomallei*, but is also referred to as *Bacillus pseudomallei*, *Bacillus whitmori*, *Flavobacterium pseudomallei*, *Pseudomonas pseudomallei*, *Pfeifferella whitmori*, and *Actinobacillus pseudomallei*.[5] It is a small pleomorphic gram-negative, rod-shaped bacterium with bipolar staining, readily isolated on all media under aerobic and anaerobic conditions. The organism is motile, with 1 or 2 flagella at 1 pole, but no spore forms are seen. No capsule has been identified on India ink preparations. *M. pseudomallei* can be differentiated from *M. mallei*, the causative organism of glanders, by its motility and its ability to attack a wider range of carbohydrate media. Colonies on infusion agar (after 24 hours at 37°C) appear as round, convex, mucoid, opaque slightly cream-colored areas. The edges of the colonies are irregular, with translucent striated peripheries and heaped-up centers. A "button shape" and "hammered-aluminum" appearance are described as being typical of the colony growth.[12] An aromatic odor has been identified as characteristic of the culture.

Pathologically, the basic lesions produced in acute melioidosis are multiple disseminated abscesses, usually minute, but frequently coalescing to form larger necrotic areas with sinus formation. They may occur in any organ but are found most frequently in the lungs, liver, spleen, kidneys, prostate, and lymph glands in descending order of frequency.[2] The abscesses are granulomas, with a central necrotic core of blood-stained pus surrounded by an area of neutrophils. Peripheral to this core is a hyperemic area containing dilated capillaries, many plasma cells, and little connective tissue. The organisms may lie within the giant cells that are usually present or may be extracellular.

CASE REPORT

A 22-year-old white man was admitted to this hospital on 1 April 1958. He had been well until about 17 March 1958, when he began to experience profuse night sweats and notice the gradual onset of aching pain in the lower lumbar region on the left side, aggravated by any motion of the spine and by coughing. The pain became progressively more severe and was accompanied by low-grade fever and chills. Two days later pain, now radiating up the patient's back to the left subscapular area, had become so severe that he was unable to bend his spine. Three days after the onset of illness similar incapacitating pain developed along the posterior and medial aspects of the right thigh. During this time the patient became aware of moderate frequency, but no change in the color or odor of his urine was noted.

The patient had lost approximately 20 pounds in the month before hospitalization. On direct questioning he stated that he had a dry, nonproductive cough, which antedated the onset of his back pain by 1 week and was accompanied by a mild frontal headache present only with motion and relieved by sitting or lying down.

At onset of his symptoms the patient was employed on a cattle ranch near San Antonio, Texas, where he had worked from 12 to 21 March 1958. During his period of employment no illness was observed in any of the cattle, and the patient had noticed no abscesses or ulcers on any of the animals. Dogs and rats were present at the ranch, but the patient denied any bites. During the course of his work, he had received many uncomplicated minor lacerations but no puncture wounds. He was not aware of having consumed any contaminated food or water.

The patient was born in Oklahoma and had lived in Arizona, New Mexico, California, Nevada, Oregon, Louisiana, Mississippi, Georgia, Florida, Kansas, Texas, Tennessee, Kentucky, Idaho, Pennsylvania, and Maryland. During his life he had worked at a variety of jobs, such as house painter, steelworker, truck driver, carpenter, and dishwasher. On 2 occasions he had used asbestos and Fiberglas as insulating materials. His habits were moderate. He had had close contact with animals only immediately prior to this hospitalization and in 1948 and 1949, when he worked as a "broncobuster."

As a child he had rubeola, varicella, and pertussis, without sequelae. In June 1954 he had gonorrhea, treated with penicillin. Serologic tests at that time were negative.

In August 1953 he enlisted in the Air Force and served in the continental United States until May 1954, when he was transferred to Korea. He was transferred to Japan in September 1954, where he remained until July 1956. At that time he returned to the United States and was discharged from the service. His only other excursions outside the continental United States had been to border towns in Mexico. Family history and system review were noncontributory.

On admission to this hospital the patient was acutely ill and thin. The temperature (oral) was 103°F, pulse rate 90 per minute, respiratory rate 22 per minute, blood pressure 116/76 mm Hg (bilateral). Ear, nose, and throat appeared normal. There was slight bilateral conjunctival injection. Pupils and extraocular movements were normal, and ophthalmoscopic examination was negative. The neck was supple. Several firm nontender slightly enlarged lymph nodes were palpable in the left posterior cervical chain. The chest was symmetric, and the lungs were clear to percussion and auscultation. Cardiac contour was normal by percussion. A grade 2 systolic murmur was heard at the apex; the pulmonic second sound was louder than the aortic second sound. There was no venous distention. Peripheral pulses were normal. Abdominal and rectal examinations were negative. There was slight pallor of the skin. Several 1-cm nontender sebaceous cysts were present on the scrotum. An exquisitely tender, reddened, subcutaneous mass, 4 cm in diameter, was found 3 cm to the left of the spine at the level of the 8th to 10th thoracic vertebrae. Any motion of the spine caused intense pain in this area. A 6- by 10-inch firm tender mass with definite signs of inflammation was noted on the posteromedial aspect of the right thigh just below its junction with the trunk. The tenderness seemed to be confined to the muscle mass and related tissues and not to involve the bone. Any movement caused excruciating pain in this area, but the process did not extend above the right inguinal ligament. The inguinal nodes were enlarged and slightly tender bilaterally. Shotty axillary nodes were also palpable bilaterally but were nontender.

On admission hematologic examination revealed a white blood cell count of

18,000 per cu mm, with 72 percent neutrophils and 27 percent lymphocytes, hemoglobin 12.4 grams per 100 ml, hematocrit 37 ml per 100 ml, corrected sedimentation rate 55 mm per hour. Urinalysis was normal and revealed a specific gravity of 1.022. The serologic test for syphilis was negative. Roentgenograms of the chest, pelvis, femurs, and lumbar and dorsal vertebrae were within normal limits, and no abnormality was noted on intravenous pyelography. An electrocardiogram was normal. Skin tests for tuberculosis, coccidioidomycosis, and histoplasmosis, using first strength purified protein derivative, 1:100 coccidioidin, and histoplasmin antigens, respectively, were negative. Blood chemistry studies revealed inorganic phosphorus of 2.5 mg per 100 ml, alkaline phosphatase (Bodansky) 2.7 units, calcium 4.8 mEq per liter, total protein 6.6 grams (albumin 4.2 grams, globulin 2.4 grams) per 100 ml, blood urea nitrogen 17 mg per 100 ml, creatinine 2.3 mg per 100 ml, and fasting blood sugar 81 mg per 100 ml.

Febrile agglutinins, drawn the day after admission, were reported as: *Salmonella typhosa* O (somatic) 1:40; *Salmonella typhosa* H (flagellar) 1:160; *Salmonella paratyphi* 1:80; *Salmonella schottmülleri* 1:80; *Pasteurella tularensis* no titer; *Proteus* OX_{19} no titer; and *Brucella abortus* no titer. The C-reactive protein was 6 plus on admission and negative on 16 April.

A lumbar puncture on 2 April revealed a clear cerebrospinal fluid with normal dynamics and an opening pressure of 130 mm of water. The Pandy test was negative, as was the serologic test for syphilis, and the total protein was 11 mg per 100 ml. There was 1 lymphocyte per cu mm and no organisms were seen on direct smear and gram stain. Spinal fluid glucose was 89 mg per 100 ml, chloride 123 mEq per liter.

Bacteriologic studies revealed negative urine and blood cultures on repeated examinations. Throat and sputum cultures revealed alpha streptococci. Material aspirated from the abscess on the right thigh revealed only *Staphylococcus aureus*, coagulase-positive, on repeated cultures.

On admission the patient was treated symptomatically with aspirin and with heat applied to the abscessed areas. Temperature remained elevated, manifesting a septic type of fever with spikes to 103°F. Needle aspiration of the tender area on the back was attempted but no material could be obtained. Aspiration of the right thigh resulted in the recovery of 4 ml of thick foul chocolate-colored necrotic material. Culture of this specimen revealed coagulase-positive *S. aureus*. Initially, it was our opinion that the patient's symptoms were related to this abscess, with a possible staphylococcic septicemia. Intravenous antibiotic therapy, consisting of 20 million units of penicillin, 2 grams of chloramphenicol, and 1 gram of streptomycin every 8 hours, was begun.

The abscess of the right thigh was opened, an 8-cm transverse incision over the medial aspect of the thigh and into the deep fascia releasing 180 to 200 ml of purulent foul greenish gray material. Cultures of this exudate grew only coagulase-positive *S. aureus*. Manual exploration of the abscess cavity revealed that it extended from just below the inguinal ligament superiorly to the inferior third of the adductor mass. The wound was left open, drains were inser ted, and the patient was then transferred to the contagious disease service for further antibiotic therapy. Inadvertently, the abscess on the back was not incised.

The day following the surgical procedure, the patient's temperature decreased to 99°F and there was subjective and objective improvement. Drainage was moderate from his right thigh, and the abscess on his back appeared much smaller and was nontender. Sensitivity studies on the material obtained during the operation revealed the organism to be sensitive to chloramphenicol and strepto-

mycin. Consequently, the previously outlined antibiotic therapy was continued. On the third postoperative day the patient was afebrile and digital exploration of the abscess cavity produced only a few milliliters of odorless purulent material. The abscess on the back had completely resolved. On the seventh postoperative day intravenous antibiotic therapy was discontinued and the patient was started on 600,000 units of procaine penicillin and 0.5 gram of streptomycin intramuscularly every 12 hours, and 0.5 gram of chloramphenicol by mouth every 6 hours. The surgical wound healed by second intention and there was no further drainage.

By 16 April (eleventh postoperative day) the patient was ambulatory and was discharged to the surgical clinic to be seen in 1 week. He failed to keep the appointment.

The diagnosis of melioidosis was suggested by one of us (E.M.) during the patient's hospitalization, but no bacteriologic confirmation could be obtained on material from the abscess cavity. On 7 April blood had been drawn and submitted to the Walter Reed Institute of Research, Washington, D.C., for complement fixation studies for *M. mallei* and *M. pseudomallei*, which were subsequently reported (after the patient's discharge) as diagnostic of melioidosis (table 1).

Table 1. ***Complement fixation test for malleomyces***

Organism	*Serum*	*Dilution*						
		1/20	*1/40*	*1/80*	*1/160*	*1/320*	*1/640*	*1/2560*
M. mallei 3873	Homologous	4	4	4	4	4	3	+
M. mallei 3873	Patient's	4	3	±	-	-	-	-
M. pseudomallei 294	Homologous	4	4	4	3	3	+	-
M. pseudomallei 294	Patient's	3	3	3	3	2	±	-

Upon receiving this report, the patient was contacted and readmitted on 20 June. He stated that since discharge from the hospital he had remained entirely asymptomatic. He had been performing heavy manual labor without difficulty. The area of incision had healed completely with no residual tenderness or drainage. Physical examination was completely negative except for a 6-inch, well-healed surgical scar over the posterior aspect of the right thigh.

The diagnosis was discussed thoroughly with the patient, who agreed to further serologic determinations. Unfortunately, he was seized by wanderlust and left the hospital before such studies could be obtained.

DISCUSSION

As no positive bacteriologic studies could be obtained in this case, the diagnosis rests on the complement fixation determinations. In a series of immunologic studies on *M. pseudomallei* Cravitz and Miller [13]

found that serum from chronic cases of melioidosis agglutinated autogenous strains in dilutions ranging from 1:80 to 1:4000. An agglutination titer of 1:80 was believed to be significant, although it was also found[13] that 97 to 98 percent of normal persons had agglutinins to *M. mallei* and *M. pseudomallei* ranging in titer from 1:10 1:320. However, a titer of 1:160 is almost certainly diagnostic of melioidosis.[14] In the series described,[13] however, complement fixation tests utilizing 400 samples of normal serums were all negative at a dilution of 1:10. The highest complement fixation titer reported in this series was 1:640. The complement fixation test became positive 4 to 6 weeks after the onset of illness, reaching its peak titer rapidly thereafter and falling off gradually as patients recovered clinically. Serums from patients hospitalized with brucellosis, tularemia, anthrax, atypical pneumonia, and infectious mononucleosis all exhibited agglutination titers within the normal range and negative complement fixation tests. It was concluded that the complement fixation test was specific for *Malleomyces* but did not differentiate between glanders and melioidosis.

In our patient, however, differential complement fixation titers were performed for both *M. Mallei* and *M. pseudomallei*, resulting in a specific diagnostic titer for *M. pseudomallei*. The agglutination test is more sensitive than the complement fixation test, but at low dilutions practically all normal serums produce agglutination. However, if normal agglutination titers have been demonstrated early in the course of illness, a progressive rise in titer may be diagnostic before the complement fixation test becomes positive.

In our patient, the complement fixation titer for *M. mallei* was positive only at a dilution of 1:40, which is considered normal. In contrast, the complement fixation titer for *M. pseudomallei* was definitely positive (3 plus) in a 1:320 dilution and equivocally positive in a 1:640 dilution. This is acceptable as proof of melioidosis by serologic criteria.[13]

Although *M. pseudomallei* is rather striking in its morphologic appearance and is easily grown in almost all culture media, several authors have commented on the relative difficulty of isolating it from large abscesses.[3,4] This is probably due to profuse staphylococcic overgrowth, plus the presence of a large volume of necrotic material. All cultures and smears obtained in our case were overgrown with *S. aureus*. It may be postulated that these factors prevented bacteriologic identification of the causative organism.

In the reported cases of melioidosis there is "no well recognized procedure to be followed in therapy." [6] Various antibiotics, singly and in combination, have been tried, as have sulfonamides, autogenous

vaccines, urea, and excision of the abscesses followed by skin grafting.[5] Early incision and drainage of the abscesses are thought to be indicated, but this seldom effects a cure and may be dangerous without concomitant antibiotic therapy.[6] Prevatt and Hunt [6] suggested that failure of antibiotic therapy in melioidosis may have been due to late diagnosis combined with small doses and short courses of antibiotics. They believe that prolonged therapy is of definite value, especially in cases with multiple metastatic foci. A review of the published cases of melioidosis has revealed no instance in which intensive massive antibiotic therapy was utilized, as in our case. Although the diagnosis of melioidosis had not been established when this therapy was begun, surgical incision and drainage of the abscess combined with intravenous administration of penicillin, streptomycin, and chloramphenicol seemed to effect an afebrile response in 3 days with healing of the abscess in 8 days. In addition, the abscess in the right paravertebral area (presumably also due to *M. pseudomallei*), although not surgically drained, cleared in 3 days on antibiotic therapy.

The patient received no further therapy following his original discharge from the hospital. Although complete evaluation could not be obtained during his second admission, he had by then been employed in strenuous physical labor for 2 months with no untoward effects and was clinically "cured." The possibility of future recrudescence cannot be excluded, but we believe that he is the first reported patient to respond in such remarkable fashion.

SUMMARY

A case of chronic melioidosis, the fifth reported from the United States, is presented. Diagnosis was established by serologic methods, and the criteria for serologic diagnosis are reviewed. Massive antibiotic therapy resulted in clinical cure.

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Porphyria Cutanea Tarda Associated With Hemochromatosis

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PORPHYRIA CUTANEA TARDA is characterized by blisters on the exposed surfaces of the skin following trauma or exposure to the sun, and by hyperpigmentation, hypertrichosis, and abnormal excretion of porphy-

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rins. Its relationship to various types of hepatic disease has often been discussed.

A patient with porphyria cutanea tarda associated with hemochromatosis was observed at this hospital. This combination of lesions has been described in the European literature [1,2] but, as far as we are aware, has not been noted in the medical literature of this country. Therefore, the following case is reported.

CASE REPORT

A 48-year-old man was seen at this hospital in October 1958, because of secondarily infected bullous lesions of the hands.

In October 1953, the patient had been obliged to give up his job as an an automobile mechanic because of recurring blisters on the hands. In January 1954, he had been hospitalized elsewhere for secondary infection of these blisters. Physical examination at that time disclosed hepatomegaly. Results of laboratory studies were not remarkable except for a 10 percent retention of sulfobromophthalein (Bromsulphalein). Biopsy of the lesions disclosed nonspecific bullae.

Bullae continued to occur on the hands, ears, and forehead, usually precipitated by trauma or exposure to the sun. The patient's general physical condition appeared excellent. His hair turned from reddish brown to black. During this period he consumed almost 1 case of beer daily. Family history was inadequate but none of his relatives were known to have been troubled by "blisters."

Examination in 1958 disclosed obesity and plethora; hyperpigmentation of exposed skin; and numerous bullae and zones of denudation on the dorsal surfaces of both hands. Cellulitis, with pronounced swelling and redness, was present in the left hand. The skin of the hands was fragile and easily detached. Small ulcerations were noted on the ears. The conjunctivas were injected. The liver was palpable 2 cm below the costal margin. The remainder of the examination was normal.

Hemoglobin was 17.5 gm per 100 ml, leukocytes 8,050 per cu mm, with a normal differential count. Erythrocyte sedimentation rate was 23 mm during the first hour (Westergren method). Urinalysis and serologic tests for syphilis gave normal results. The fasting blood sugar level was normal. A roentgenogram of the chest was normal. Liver function tests showed 30 percent retention of Bromsulphalein, thymol turbidity 5.8 units, cephalin-cholesterol flocculation 1+. Serum albumin measured 4.8 grams per 100 ml and serum globulin 2.9 grams per 100 ml. Cutaneous biopsy demonstrated chronic bullous dermatitis.

The patient's condition was diagnosed as porphyria cutanea tarda accompanied by fairly advanced impairment of hepatic function. He was advised to reduce his alcohol intake, follow a dietary regimen for cirrhosis, avoid the sun, and wear gloves while working. He received antibiotics locally to prevent secondary infection of the blisters, which continued to recur.

In March 1959, he was again admitted to the hospital because of secondary infection of the blisters on his hands. Examination revealed the presence of bullae on the exposed skin, which had a violaceous hue. The skin of the hands was still fragile. Numerous milia were observed on the healed areas of the hands. Blood pressure was 136/84 mm Hg. Conjunctivitis was evident. The heart and lungs were not remarkable. The edge of the liver was easily felt 5 cm below the right costal margin. The spleen was not palpable.

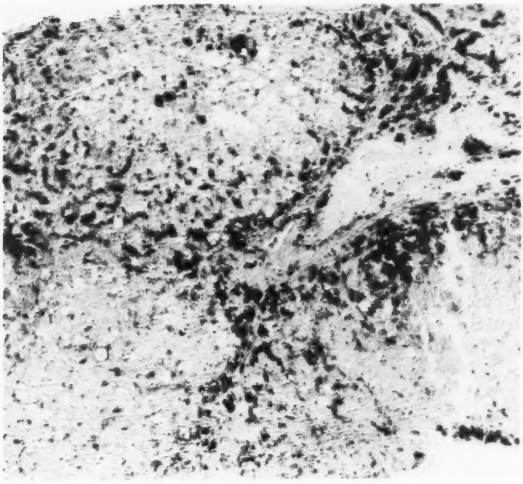

Figure 1. Extensive hemosiderosis within widened irregular portal tracts and dispersed through hepatic cells, together with minimal active portal cirrhosis, suggests diagnosis of hemochromatosis. (Gomori iron stain, x 100)

The leukocyte count was 6,100 cells per cu mm, hemoglobin 17.4 grams per 100 ml, hematocrit 50 ml per 100 ml. There was 29 percent retention of Bromsulphalein in 45 minutes. Serum protein measured 6.9 grams per 100 ml. Serum bilirubin was 0.8 mg per 100 ml, of which 0.2 mg was direct and 0.6 mg indirect; thymol turbidity 2.4 units. Prothrombin activity, as indicated by a prolonged prothrombin time, was 89 percent of normal. Bleeding time was 1.35 minutes, and coagulation time 5.45 minutes. The urine showed fluorescence in ultraviolet light. Urine coproporphyrins and uroporphyrins I and III were repeatedly and greatly increased in amount. Biopsy of cutaneous lesions showed acantholytic subepithelial bullae.

Biopsy of the liver disclosed portal cirrhosis with hemosiderosis. The presence of large amounts of hemosiderin in the widened irregular portal tracts and finely dispersed within the hepatic cells, together with minimal active portal cirrhosis, suggested the diagnosis of hemochromatosis (fig. 1).

Further studies to corroborate this diagnosis revealed the following: normal glucose tolerance; serum iron 175 micrograms per 100 ml, with total iron-binding capacity of 225 micrograms per 100 ml, a saturation of 78 percent; strongly positive Gomori iron stain of the liver, negative iron stains of the skin; normoblastic erythroid hyperplasia of bone marrow, with excessive deposition of iron pigments. The clinical impression was porphyria cutanea tarda associated with hepatic disease, probably hemochromatosis; the laboratory data appeared to be consistent with this diagnosis.

DISCUSSION

Watson [3] has outlined the types of porphyria according to their clinical features, as follows:

A. Porphyria erythropoietica: childhood photosensitivity, increased hemolysis and erythropoiesis, splenomegaly; excessive and abnormal formation of porphyrins in developing erythrocytic series in bone marrow
B. Porphyria hepatica: adults; excessive and abnormal formation of porphyrin precursors and porphyrin in liver
   1. Intermittent acute type: young adult females predominate; abdominal or nervous manifestations or both
   2. Cutanea tarda type: older males predominate; low-grade photosensitivity, melanosis, hirsutism, and frequent hepatic dysfunction
   3. Mixed or combined: symptoms of both types above

The patient presented a clinical picture in keeping with porphyria cutanea tarda and hemochromatosis. Blistering of the skin in response to light or trauma, melanosis of exposed surfaces, change in color of the hair from red to black, and appearance of milia in areas of healing, are typical of this disease. Fluorescence of the urine, associated with an increase in uroporphyrins and coproporphyrins, and the histologic appearance of the cutaneous bullae further support this diagnosis. Hepatomegaly and impairment in hepatic function led to biopsy of the liver, the macroscopic appearance of which strongly suggested hemochromatosis. Further studies tended to substantiate this impression.

Hemochromatosis is an uncommon disease characterized clinically by cirrhosis of the liver, cutaneous pigmentation, and diabetes mellitus, although all these features need not be present. It most likely represents an inherited intestinal block, leading to increased absorption and excessive accumulation of iron in body tissues, associated with diffuse fibrosis. Pigmentation varies from slate gray to brown and is most noticeable on the face, forearms, axillae, and dorsal aspects of the hands. Hypogonadism and absence of axillary and pubic hair are also common.

Laboratory studies useful in establishing the diagnosis include examination of bone marrow, epithelial cells of sweat glands, and urinary sediment for iron. Serum iron is usually increased, as is the percentage saturation of the iron-binding protein, siderophilin [4,5]. Hepatic biopsy is of course most helpful.

The literature contains considerable evidence that porphyria cutanea tarda is secondary to hepatic disease in many patients. Most patients are men who give histories of hepatic damage. Schmid and associates [6] found that many patients in their hepatic porphyria group showed impairment of hepatic function, particularly those with the

cutanea tarda type. Of 12 such patients, 6 had abnormal hepatic tissue on biopsy, and 10 had impaired hepatic function. Brunsting [7] studied 34 patients with porphyria cutanea tarda, 25 of whom showed some degree of hepatic impairment. Analyzing 80 patients with hepatic porphyria, Martin and Heck [8] found 32 whose Bromsulphalein test revealed grade 2 (12 to 22 percent) or more dye retention. Lang and Walker [9] reported 5 patients with cutaneous manifestations of porphyria, 4 of whom showed severe disturbance in hepatic function. These investigators thought that the histologic findings in the liver were nonspecific. Porphyria and hepatic disease are often associated in the Bantus of South Africa. Barnes [10] reviewed 113 Bantu patients with porphyria, most of whom had cutaneous lesions. Of 69 of these patients in whom an assessment of the liver was performed, 34 had hepatomegaly.

In all but 1 of 36 patients with porphyria cutanea tarda, Berman and Bielicky [11] found chronic alcoholism as a background. Studying 2 patients with porphyria cutanea tarda following infectious hepatitis, Tulloch and Warin [12] thought that hepatic damage led to an alteration of the already disordered porphyrin metabolism, with production of high porphyrin levels. On the other hand, Tio and his coworkers [13] studied a patient in whom a benign liver cell adenoma was associated with pathologic excretion of porphyrins and development of the clinical picture of porphyria cutanea tarda; removal of the tumor led to cessation of symptoms.

In 1956, Brugsch [14] reported 4 patients who had what he called "melanodermic porphyria." These patients had diffuse dark discoloration of the skin but did not present bullous cutaneous lesions or symptoms of acute intermittent porphyria. Uroporphyrins I and III were found in the urine in abundance. Alcoholism was prominent in the histories. Histologically, the liver showed varying amounts of cirrhosis and considerable siderosis. Brugsch and associates [15] reported another such case in 1957. In 1958, Brugsch [16] reported 3 more patients with melanodermic porphyria associated with pigmented cirrhosis and diabetes mellitus. These 8 patients demonstrated many of the characteristics of porphyria cutanea tarda and hemochromatosis, but Brugsch thought that they represented a distinct entity.

The association of hemochromatosis and porphyria cutanea tarda has been noted previously in the European literature. Of 9 cases of cutaneous porphyria presented by Bolgert and coworkers,[2] 6 had hepatomegaly, and 8 had increased serum iron. Biopsy of the liver was reported in only 1 patient, who had hepatic changes consistent

with hemochromatosis, associated with diabetes mellitus. These authors thought that an error in iron metabolism, with excessive amounts of serum iron and excessive deposition of iron in the liver, was perhaps a special characteristic of cutaneous porphyria. Langhof and Mildschlag [1] reported a 47-year-old man who after minor trauma had blisters on the areas of skin exposed to light. Laboratory studies revealed elevated uroporphyrins and coproporphyrins, large amounts of serum iron, impaired hepatic function, and pancreatic insufficiency.

The simultaneous occurrence of cirrhosis of the liver and porphyria raises the question whether the abnormal metabolism of porphyrins may enhance the development of cirrhosis or whether the hepatic disease produces the disturbances in porphyrin metabolism. A defect in hemosynthesis is perhaps the primary factor, leading in some patients to both porphyria and hemochromatosis. Many investigators believe that hepatic damage activates an inborn error of metabolism, resulting in abnormal excretion of porphyrins.

SUMMARY

A case of porphyria cutanea tarda associated with hepatic disease, probably hemochromatosis, is reported. The clinical and laboratory data were consistent with the diagnosis. The exact relationship of hepatic disease to porphyria cutanea tarda has not been established. Of interest is the association in the same patient of 2 diseases in which iron metabolism and hemosynthesis are concerned.

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VITAMINS AND POISON

Consider the metabolic quirk that makes a poison of folic acid. If a patient with pernicious anemia is given folic acid instead of vitamin B_{12}, his anemia is corrected, but the central nervous system changes continue to progress, in fact they may be accelerated. . . . It is easy to decide that the peevish old lady who complains of fatigue should be given a "tonic" of some sort, perhaps vitamin pills. But wait a moment. Once in a while, the peevish old lady has pernicious anemia and because of the folic acid in her vitamin pills she may spend the rest of her life incontinent of urine and feces, fast in a wheelchair. . . . The problem is not a large one in terms of numbers but fortunately it is a problem that has a solution: *omit the folic acid from multivitamin preparation.*—WILLIAM H. CROSBY: The Danger of Folic Acid in Multivitamin Preparations. *Military Medicine*, April 1960.

Technical Notes

Multiple Checkerboard Targets for Testing Visual Acuity

IRA SCHWARTZ, O.D.
SAUL M. LURIA, PH.D.

DEVICES FOR TESTING VISUAL ACUITY have taken many forms. Almost all suffer from the possibility that the subject may memorize them and that factors other than retinal resolution may affect the results. An extensive analysis [1] has revealed that the factors of form, brightness, configuration, and literacy are present in most acuity measures, but that checkerboard-type targets are least influenced by these variables.

As is well known, this type of target presents 4 squares of the same size arranged in the form of a diamond on a white card. Three of these squares are formed of closely spaced dots and when viewed at a distance appear as uniform gray patches. The fourth square is composed, checkerboard fashion, of black and white checks of equal size. All 4 corners of the checkerboard square are black. When the subject cannot resolve the checkered square, it appears as a gray patch like the 3 others. The subject's task is to locate (as top, bottom, left, or right) the square that is different in the group of 4.

Morris and Dimmick [2] reported the first use in this laboratory of this type of target. Thirty sizes of checkered squares from 5.4 to 67.4 mm were used. The checkerboard was held in a detachable clip and was changed by hand. This was suitable for the research program then undertaken. Morris, Katz and Bowen [3] reported an improved target design and described an apparatus for presenting 1 target at a time mounted on the end of a revolving shaft that could be rotated by a remote control mechanism.

Faced with the problem of providing an acuity test useful in scientific experimentation and in screening large groups of subjects, we have designed an apparatus to present multiple targets simultaneously and to change them in a manner to circumvent memorization by the

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From U.S. Naval Medical Research Laboratory, U.S. Naval Submarine Base, New London, Conn. Memorandum Report 60-3.

subjects. The apparatus described in this report also makes the test easy to administer and reduces the subjects' waiting time between target exposures.

DESCRIPTION OF APPARATUS

The apparatus developed presents 5 targets at once (fig. 1). Each target is mounted on the end of a shaft and is readily detached to allow rearrangement of the 5 targets. Rotation of the targets is such that 3 move clockwise and 2 counterclockwise to minimize memorization during the test session. Repeated testing of a subject is thus possible since order and orientation can readily be varied as frequently as necessary.

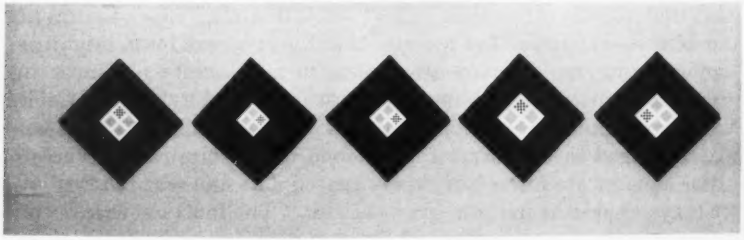


Figure 1. Multiple checkerboard acuity tester presenting 5 targets simultaneously.

The control panel (fig. 2) has a selector switch and 4 indicator lights for each target. These lights show the respective positions of the checkerboard at the setting represented (fig. 1). The display positions of the targets can be changed by altering the contacts.

Figure 3 shows 2 views of the back of the apparatus, which consists basically of a motor and its drive shaft, to which are geared the 5 target shafts (fig. 4). On the end of the main shaft is a cam moving against 4 normally open microswitches and so designed that only 1 of the switches is open at a time. A solenoid operates a clutch and a braking mechanism on the shaft. Both of these were found necessary to ensure proper positioning of the targets.

With the control switch moved to a new position, current flows through the appropriate microswitch to the rectifier, which activates the relay, completing the circuit to both the solenoid and the motor (fig. 5). The solenoid then releases the brake on the shaft and activates the clutch, allowing the motor to turn the shaft. The shaft

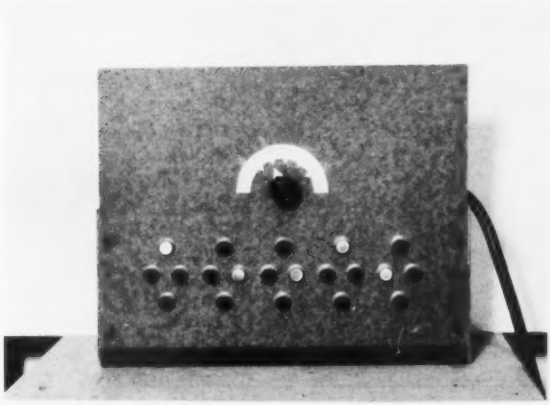
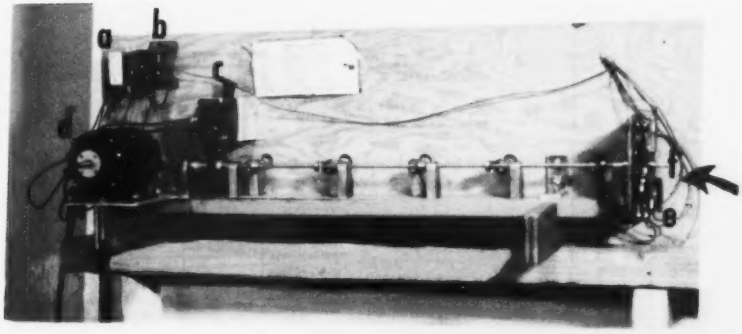


Figure 2. Control panel of visual acuity tester has selector switch and indicator lights for each target.



a Relay
b Rectifier
c Solenoid (brake & clutch)
d Motor
e Microswitches (4)
f Cam

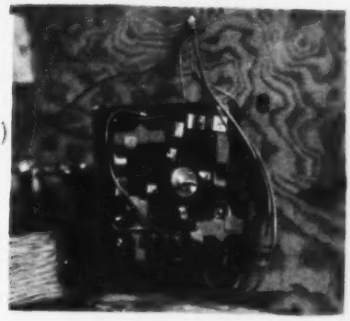


Figure 3. Back view of apparatus.

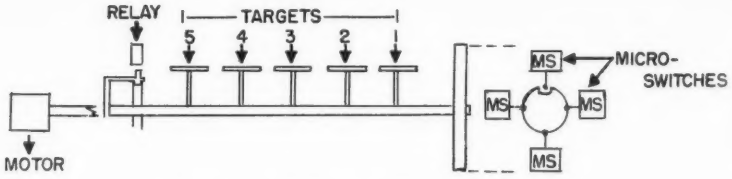


Figure 4. Schematic diagram of apparatus.

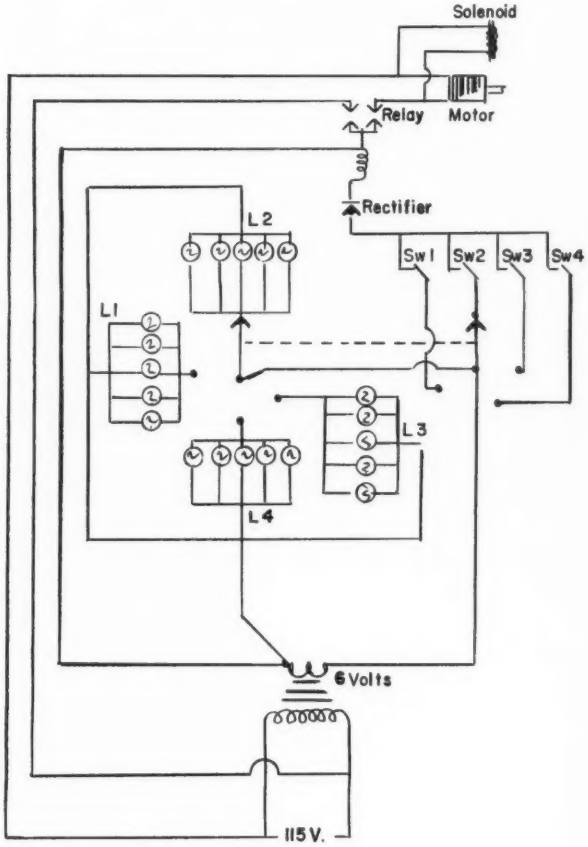


Figure 5. Schematic wiring diagram.

continues to rotate until the cam reaches the activated microswitch. When the switch falls into the depression on the cam, the circuit breaks, simultaneously cutting off the current to the motor, releasing the clutch, and applying the brake. When the control switch is moved to another position, a new microswitch is activated and the chain of events is repeated.

APPLICATIONS OF APPARATUS

The apparatus can be used in various ways. For a simple pass-fail examination, all targets may be of the same size. Two positions of the control switch will thus present 10 targets, 9 of which, for example, the examinee would have to see correctly to pass. To determine a limen, a graded series of target sizes would be used. The sizes would be chosen and a program of positions would be formulated in advance so that the smallest would be seen about 10 percent of the time while the largest would be seen about 90 percent of the time. The percentage seen for each of the 5 targets would then be plotted against the target size to give a seeing frequency curve, with the 50 percent point taken as the limen. This apparatus is useful not only for testing large numbers of subjects, but lends itself to many research needs.

SUMMARY

An apparatus for testing visual acuity developed in this laboratory is described. Presenting 5 checkerboard targets simultaneously, this apparatus circumvents memorization by the subjects. Possible applications include simple pass-fail examinations and determination of limens. It is expected that the device will be useful for screening large numbers of subjects and for research purposes.

ACKNOWLEDGMENT: The development and construction of the mechanical apparatus was greatly aided by the suggestions and skill of Oskar Dengler of the apparatus shop of this laboratory.

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Diagnostic Head Light for Ocular Muscle Testing

MAJOR THOMAS J. TREDICI, USAF, MC

AS AN OPHTHALMOLOGIST I have found the light described here an extremely helpful tool. This versatile piece of equipment is hidden under the guise of an ENT tool in the supply catalog,[1] where it is listed as #6515–340–8100—Light, head, diagnostic, and #6515–318–6840—Power supply, cautery apparatus, medium. The apparatus described are all standard items easily obtainable through medical supply. Although other diagnostic lights are described in the literature,[2] this one has advantages of simplicity and ready availability. Some ophthalmologists may already be using this tool, but it is also recommended for use by flight surgeons, in emergency rooms and for visual screening examinations.

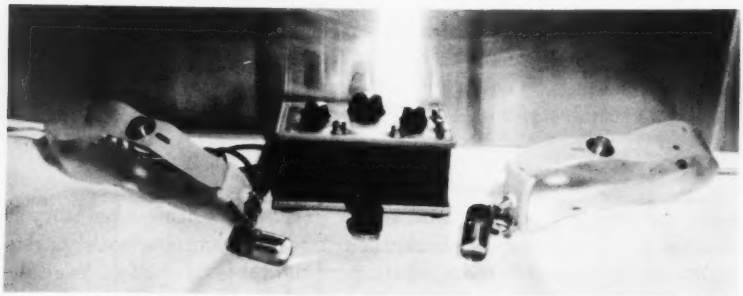

Figure 1. The head light adjusted for muscle testing (left) and for examination and surgery (right). The standard 6-volt transformer and removable mirror are shown in the center.

To convert the light to an ophthalmic tool the mirror is removed. For use in muscle testing the light is adjusted as shown in figures 1 and 2, with the beam coming from the lowest point of the universal bracket. To test the muscles in the 6 cardinal directions the examiner keeps his head and the light in a fixed position and simply turns the patient's head. The corneal reflex is bright and by focusing the light the illuminated area can be increased or decreased. This will be found useful in examining patients with a dark-brown iris.

From U.S. Air Force Hospital Clark, APO 74, San Francisco, Calif.

Figure 2. Diagnostic light used for muscle testing. Both hands are free for handling the prisms and occluder.

The use of the light for external examination of the eye, minor surgery, and foreign body removal is shown in figure 3. For such procedures the universal bracket is adjusted so that the light is at

Figure 3. Diagnostic light used with a loupe for external examination and minor surgery.

the top (fig. 1). If a loupe is used the beam is focused at the focal distance of the loupe. This is a better light source than a fixed wall or floor light, especially in examining or performing minor surgical procedures on infants, who frequently move from the area of the fixed beam.

A 6-volt bulb should be used with the standard transformer (fig. 1). If one requires a more intense source of illumination, a 3.8-volt bulb such as that used in a 3-cell flashlight can be substituted. Under such circumstances, however, the life expectancy of the bulb will be shortened.

SUMMARY

A readily available diagnostic ophthalmic light source is described. Brief instructions for its use are given.

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NEGLECTED AREA

Many doctors regard the obese patient as a neurotic nuisance and the diet treatment as a complicated bore. They dismiss obese patients with a few general admonitions, a printed list of foods, and a medication. Seldom does a physician give an obese patient's diet problems the attention that might be applied to regulating insulin for patients with diabetes or diuretics for those with heart disease. . . . The emergence of so many nonmedical individuals as guides in the treatment of obesity has been due in part to the large popular demand and in part to the disinterest and apathy of many physicians.—Alvan R. Feinstein: The Treatment of Obesity, an Analysis of Methods, Results, and Factors Which Influence Success. *Journal of Chronic Diseases,* April 1960.

THIS ISSUE of the *U.S. Armed Forces Medical Journal* includes the first of a series of reports describing the recent work of the Armed Forces Epidemiological Board (AFEB). This first report, by Dr. William S. Jordan, Jr., Professor of Preventive Medicine, University of Virginia School of Medicine, reviews the current work of the Commission on Acute Respiratory Diseases, of which he is director. In a succeeding issue of the *Journal*, Dr. Fred M. Davenport, director of the Commission on Influenza, will review the research of his group from 1959 to 1960. Subsequent reports will be prepared by the directors of the other 10 commissions of the Armed Forces Epidemiological Board.

In the near future, Colonel John Rizzolo, USAF, MC, Executive Secretary of the Board, will describe the consultative and operational relationships of the Board and its commissions with the military medical services. Colonel Rizzolo will also review the research in preventive medicine accomplished between 1956 and 1959, sponsored by the Armed Forces Epidemiological Board, most of it supported by the Army's surgeon general through his Medical Research and Development Command.

So that its readers may be fully aware of the activities of the AFEB, from time to time throughout the year the *Journal* will publish original articles on research in progress and on scientific accomplishments sponsored by the Board or abstracts of articles to be published elsewhere. Thus, through this publication—a unique medium for the dissemination of military medical knowledge—a vast and constantly growing store of information of vital importance to military medicine will become immediately accessible.

It is our aim and hope that by means of such reports, articles, and abstracts members of the military medical services will be provided with current knowledge about major medical problems and about the contributions that the Board and its Commissions are making toward their solution.

GUSTAVE J. DAMMIN, M.D.
PROFESSOR OF PATHOLOGY, HARVARD MEDICAL SCHOOL
PRESIDENT, ARMED FORCES EPIDEMIOLOGICAL BOARD

This article was already in press when the decision to cease publication of the *Journal* in December 1960 was reached. AFEB Commission reports will appear in the November and December issues of the *Journal*.—EDITOR.

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Activities of the Commission on Acute Respiratory Diseases

WILLIAM S. JORDAN, JR., M.D.

SINCE ITS ORGANIZATION during World War II, the Commission on Acute Respiratory Diseases has been concerned with the variety of microorganisms—viral, bacterial, rickettsial, fungal—that produce acute respiratory infections in man. Three recent reports [1-4] from Commission investigators—concerned with the common cold, streptococcic infections, and coccidioidomycosis—have presented some of the new data that are accumulating in this broad attack on respiratory pathogens. These reports are summarized briefly here for the information of the military services, and to illustrate the type of studies currently of interest to the Commission.

For the past 8 years, Drs. Harry F. Dowling, George Gee Jackson, and associates [1] at the University of Illinois have been studying the results of experimental challenge of volunteer subjects with common cold agents. Secretions from donors with naturally acquired common colds have been filtered and administered to over 2,500 subjects. The experimental illnesses produced resembled those resulting from natural infection. The predominant features were afebrile coryza; different viruses produced a greater or lesser degree of noncoryzal pharyngitis and occasionally a febrile respiratory infection. Dilution of the secretions over the range 1:10 to 1:100 caused no significant change in the frequency or the severity of the colds. In a dilution to 1:1,000, infectivity was lost. Under experimental conditions neither total body chilling nor frigid conditions induced spontaneous infections or increased susceptibility to experimental infection. Sleep deprivation and fatigue increased infectivity insignificantly. Female subjects showed differences in susceptibility in relation to different

From the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Washington, D.C. Dr. Jordan, director of this Commission, is at the University of Virginia School of Medicine, Charlottesville.

phases of the menstrual cycle, susceptibility increasing after cessation of menstruation and reaching a peak in the immediate preovulatory period. A second peak of high susceptibility to induced colds appeared to occur in the immediate premenstrual phase. Previous tonsillectomy had no influence on either susceptibility or symptoms. Immunity to specific common cold viruses was shown by rechallenging volunteers with the same infectious nasal secretions. Using secretions collected in 5 different years, no heterologous immunity was shown; it was assumed, therefore, that a different virus is present in each secretion. To date, these viruses have not been grown in the laboratory. Pooled human gamma globulin neutralized infectivity of several viruses associated with natural common colds. These data confirm earlier studies of the Commission on Acute Respiratory Diseases and studies of other investigators that indicate that the common cold is a virus infection. They further suggest that the common cold is a syndrome that may be caused by a number of specific viral infections, each of which elicits an appropriate immune response.

For over 12 years, Dr. John H. Dingle and his associates [2] at Western Reserve University have been conducting a study of illness in a group of Cleveland families. These investigators have documented the frequency of nonbacterial respiratory infections, and have provided detailed descriptions of the epidemiologic behavior of the common respiratory diseases, influenza, and adenovirus infections. Although illnesses due to group A streptococci constituted only about 3 percent of the respiratory illnesses seen in the Cleveland population, the longitudinal nature of the investigation provided an opportunity for analysis of the epidemiology of the acquisition of such streptococci. Acquisition of group A streptococci most commonly occurred during January through June, rates being higher among young school children. Once a group A streptococcus was acquired, there was a 40 percent rate of streptococcic illness, with types 4 and 12 resulting in higher illness rates as well as being the most common types isolated in the study. Children acquired significant clinical illness only 1⅓ times as frequently as their parents. The group A streptococcus was most commonly introduced into the family by school children, 6 times as frequently as by their parents. The secondary carrier rate was 25 percent when the index carrier had a streptococcic illness, but was only 9 percent when the index carrier did not have such an illness. Although there was a relatively high rate of spread of the organisms when they were introduced into the household, the spread of streptococci in a family unit often occurred quite slowly. Following acquisition, the carrier state frequently persisted for a

long time. In view of the potential seriousness of streptococcic disease and its complications, the Cleveland investigators recommend the administration of penicillin in an amount and for a period sufficient to eradicate streptococci from other members of the family once the initial case has been recognized or once it is known that pathogenic streptococci have been introduced into a household.

The third report [3,4] represents the collaborative effort of investigators from a military installation—U.S. Naval Medical Research Unit No. 1—and from both the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases. Dr. Charles E. Smith of the University of California long has provided skin test coccidioidin to the armed services and the 2 papers cited provide valuable data regarding the behavior of this material in man. Using methods developed by Dr. H. S. Lawrence of New York University, it was shown that generalized delayed sensitivity to coccidioidin can be transferred from person to person with leukocyte extracts obtained from sensitive donors and treated with desoxyribonuclease. The results of transfer of coccidioidin sensitivity by this means generally paralleled those obtained in man following transfer of bacterial hypersensitivity using extracts of specifically sensitized donor leukocytes. When used as a skin test reagent, coccidioidin alone did not induce delayed sensitivity to itself. Repeated intradermal coccidioidin testing of reactors with weak or latent sensitivity sometimes effected an anamnestic delayed reactivity to coccidioidin. It was shown that healthy subjects living in an area endemic for coccidioidomycosis may exhibit delayed allergy to the coccidioidin in the absence of detectable serum complement-fixing antibody; and, occasionally, serum antibody may be present in such subjects without delayed allergy to coccidioidin. These findings suggested that the delayed type of allergic inflammatory response to coccioidin need not necessarily be correlated with the presence or absence of serum antibody—another parallel between fungal hypersensitivity and bacterial allergy of the tuberculin type.

Other investigators of the Commission are studying the growth of viruses in tissue culture systems, the chemical nature of virus antigens, specific immune responses, radiation, nonspecific serum factors and host resistance, and a diversity of other problems. Respiratory diseases remain the chief cause of illness in both military and civilian populations. The ultimate goal of these studies, as well as the ones summarized here, is the prevention and control of respiratory infections. The Commission on Acute Respiratory Diseases will continue its efforts to contribute to progress toward this goal.

AFEB COMMISSION ON ACUTE RESPIRATORY DISEASES

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THE ANXIETY OF NOTHING TO WORRY ABOUT

The so-called low toxicity of any tranquilizer may represent a psychological hazard. In other words, the anxious patient may become more anxious because he no longer feels anxious while taking a tranquilizer! He worries because of his lack of worry and he feels that there is "a catch in it somewhere." In short, natural anxiety may be a normal defense mechanism and therefore have virtue in its own right. When anxiety is suddenly and completely removed by the administration of a tranquilizing agent, the patient promptly finds himself at sea and utterly confused by a situation with which he cannot cope. He, therefore, must substitute a more normal defense mechanism, if he can summon one, or fall flat on his face.—CHRISTOPHER C. SHAW and PHILIP W. FELTS: Treacherous Tranquilizers. *American Journal of the Medical Sciences*, February 1959.

This portrait of General Kirk was reproduced from a drawing by Herman Van Cott, chief of the Medical Illustration Service, Armed Forces Institute of Pathology, Washington, D.C. Mr. Van Cott is a graduate of Yale University School of Arts and Architecture, class of 1924.

Major General Norman Thomas Kirk
1888-1960

Major General Norman Thomas Kirk, surgeon general of the U.S. Army during World War II, died 13 August at Walter Reed General Hospital, Washington, D.C., at the age of 72.

During his tenure as surgeon general, General Kirk, recognized as one of the country's foremost experts on bone surgery, headed the largest medical service in U.S. history. Under his guidance, the Army Medical Corps in the second World War increased from 1,200 to a peak of 47,000 physicians, with 15,000 dentists, 57,000 nurses and more than a half million auxiliary medical and administrative personnel caring for some 15 million patients.

Born in Rising Sun, Md., 3 January 1888, the general received his medical degree from the University of Maryland School of Medicine in 1910, and served as resident physician at the University Hospital, Baltimore, Md., and as clinical assistant at the U.S. Soldier's Home Hospital, Washington, D.C., before becoming a member of the Regular Army Medical Corps in 1913.

Proceeding from general surgery to bone and joint surgery in 1919, General Kirk was credited with treating nearly a third of the major amputations incurred in World War I. In 1924 he published "Amputations: Operative Techniques," a volume still recognized as a standard work. In 1942 the general directed the conversion of the 1,750 bed sanitarium at Battle Creek, Mich., to Percy Jones General Hospital and became its commanding general.

General Kirk was named surgeon general of the Army in 1943, a post he held until his retirement in 1947. Under his leadership, the number of Army deaths from disease decreased from a World War I rate of 165 per 10,000 patients to 60 per 10,000. There were no cases of yellow fever, and although troops fought through areas infested with typhus, cholera, and plague, they escaped these diseases almost entirely. During the heavy fighting in Europe, the general made 3 inspection tours of medical facilities with Secretary of War Henry L. Stimson, and accompanied President Truman to the Potsdam Conference as his personal physician.

In addition to other assignments during his 35 years of military service, General Kirk served as chief of either the Surgical or Orthopedic Service at the U.S. Station Hospital, Fort Sam Houston, Texas; Sternberg General Hospital, Manila, P.I.; Walter Reed General Hospital, Washington, D.C., U.S. Station Hospital, Fort Mills, Corregidor, P.I.; and Letterman General Hospital, Calif.

He was a diplomate of the American Board of Surgery, a fellow and governor of the American College of Surgeons, a fellow of the American College of Physicians, and a member of the Association of Military Surgeons and many other medical societies.

The general received the Outstanding Alumni Award from the University of Maryland in 1958. He held the Legion of Merit, the Distinguished Service Medal, the French Cross Legion of Honor, and the ranks of commander of the Order of the British Empire and commander of the Order of the Crown of Italy.

General Kirk was buried with full military honors on 16 August at Arlington Cemetery, Arlington, Va.

This Is Your A. M. A.

THE CURRENT AND CONTINUING FUNCTION of the Council on Medical Education and Hospitals of the American Medical Association—and the function of greatest importance—is the development and maintenance of high standards of medical education: in college preparation for medical study, in medical school itself, in the internship and residency, in continuing education for physicians throughout their professional lifetimes, and in education in allied professional fields. Other Council activities are in one manner or another related to this primary function. The concern is with elevation of standards of education rather than with the standardizing of educational programs. Experiments in education that are thoughtfully planned and implemented are encouraged, even when they represent considerable departures from traditional curricula and approaches. The Council continues to be concerned with the survey of existing and proposed educational programs.

The Council serves as a central reference source of information and consultation related to all areas of medical education. It collects and publishes each year information on basic medical education, internship and residency training programs, postgraduate continuing study opportunities, and medical licensure statistics. Hence, 4 special numbers of the *Journal of the American Medical Association* annually carry reports of those studies, which provide unique data.

Another aspect of this kind of activity is the planning and implementation of the Annual Congress on Medical Education and Licensure, in cooperation with the Advisory Board for Medical Specialties and with the Federation of State (Licensing) Boards. The Congress has for its purpose the provision of a forum for full discussion of issues of contemporary importance to medical education and licensure.

In concert with the Association of American Medical Colleges, the Council has directed study and informational activities toward expanding educational facilities in medicine to meet the demands of an increasing population having greater health consciousness. A related activity is the development and wide dissemination of more adequate career information about medicine for high school students, in order that a greater number of the most capable young people may be attracted into the field of medicine. Neither existing medical schools nor those yet to be founded can function effectively without an adequate pool of applicants from which to select their student bodies.

A Special Study Committee of the Council, composed of members of the Council, the Board of Trustees, the House of Delegates, and representatives of medical schools, has under study the problem areas important to consider if the profession is to continue to provide necessary leadership to meet future needs. These problems include the attraction of a greater number of capable students into medicine—perhaps by the provision of scholarships; the provision of new medical schools; augmentation of faculty personnel; and the problems of financing new schools and expansion of present ones.

There is in progress the development of a graduate program to better prepare physicians of the future for family practice.

From the Council on National Security of the American Medical Association. The views and opinions expressed are not necessarily those of the Department of Defense.—EDITOR.

The Educational Council for Foreign Medical Graduates, Inc.—an evaluation mechanism for foreign medical graduates, replacing the list of foreign medical schools formerly published jointly by the Council and the Association of American Medical Colleges—was developed under sponsorship of the Council in cooperation with the Association of American Medical Colleges, the American Hospital Association, and the Federation of State Boards.

A brief historical note will give greater insight into the structure and functions of the Council. It was established in 1904 as a standing committee of the A.M.A. House of Delegates to provide continuity of thought and action lacking in the Committee on Medical Education appointed in 1848, a year after the Association itself was founded. On its establishment, the Council on Medical Education was charged to make an annual report to the House of Delegates on the existing conditions of medical education in the United States, to make suggestions as to means and methods by which the A.M.A. might best favorably influence medical education, and to act as the agent of the American Medical Association (under instruction from the House) in its efforts to elevate medical education.

The original Council consisted of 5 physicians, who were leaders in medical education from 5 of the best schools, elected by the House of Delegates, with a staff consisting of 1 full-time secretary, also a physician. The Council now consists of 10 physicians—including those in private practice as well as medical educators—elected by the House for 5-year terms, and a professional staff of physicians and nonmedical assistants and clerks.

When the Council began its work in 1905, medical education in the United States was in a chaotic condition. There were 160 so-called medical schools, few of which had reasonable minimum educational requirements for admission of students or for their selection, or minimum standards for the medical course itself. This situation required the entire attention of the Council initially, in cooperation with the state licensing authorities and the Association of American Medical Colleges. Educational standards were prepared after conferences had been held with the best medical educators. Schools were inspected and graded, and the ratings were published. Many closed or were consolidated with others.

Eight years later it was possible for the Council to begin devoting similar attention to the internship. This resulted in the publication of lists of hospital internships beginning in 1914. The period of post-internship training for a specialty later occupied the attention of the Council on Medical Education. The 15 committees—each consisting of specialists of recognized stature in their fields—appointed in 1919 to recommend standards for education to enter a specialty field led to the formation of all the American specialty boards except ophthalmology, which had formed its board in 1917. Each board is separately incorporated and relatively autonomous.

With its activities involving hospitals as well as medical schools, the words "and Hospitals" were added to the Council's name in 1920 by the House of Delegates. The Council began listing hospitals meeting minimum standards for patient care, and a list of registered hospitals was published annually in the *Journal of the American Medical Association* from 1921 to 1954, by which time the Joint Commission on Accreditation of Hospitals was functioning effectively. The first list of approved residency programs was published in the *J.A.M.A.* in 1927 in conjunction with the list of approved internships.

Both internship and residency programs are visited at least every 3 years by professional representatives of the Council. Information secured from the hospitals and from the surveyors is evaluated by review committees, usually

consisting of representatives of the Council and of the specialty board concerned. Thus, the specialty training programs are actually approved by specialists of recognized stature in each field.

The development of the so-called allied professional areas and their importance to modern medical care has also occupied the attention of the Council and its staff, in cooperation with appropriate national organizations of the groups concerned. Such fields include medical and x-ray technology, physical and occupational therapy, and medical record librarianship.

The important role of the *Journal of the American Medical Association* in establishing the wide influence of the Council cannot be overemphasized. Wide dissemination of the Council's findings, classifications, policies, and recommendations in the *J.A.M.A.* have been of inestimable value in making effective the work of the Council on Medical Education and Hospitals.

Dr. John B. Youmans Gets AMA Post

Dr. John B. Youmans, technical director of research, U.S. Army Medical Research and Development Command, has been named director of the American Medical Association's Division of Scientific Activities. He will assume full-time duties at the American Medical Association office in Chicago in October. As new head of a division that was created in 1959, Dr. Youmans will coordinate all scientific activities of the AMA.

In his present position with the Army Medical Research and Development Command since September 1958, Dr. Youmans is a graduate of Johns Hopkins School of Medicine, receiving his degree in 1919. He was commissioned in the Army Medical Service in 1944 and later served as chief of the Nutrition Division of the Preventive Medicine Service in the Office of the Army Surgeon General, conducting nutrition surveys in China and in the Pacific and European Theaters. For his service he was awarded the Legion of Merit.

Retiring from the Army in 1946, Dr. Youmans became dean and professor of medicine at the University of Illinois College of Medicine and served in the same capacity at Vanderbilt University School of Medicine from 1949 until his resignation in 1958.

He is a fellow of the American College of Physicians and a member of the American Medical Association, American Clinical and Climatological Association, American Society of Clinical Investigation, Association of American Physicians, and Society for Experimental Biology and Medicine.

New Books

Books received by the U.S. ARMED FORCES MEDICAL JOURNAL *are listed in this department for the information of readers, and as acknowledgment and appreciation of their receipt from the publishers. Those of greatest interest will be selected for review in a subsequent number of the* JOURNAL.

AMERIKA SAMOA, A History of American Samoa and Its United States Naval Administration, by Captain *J. A. C. Gray*, MC, USN. 295 pages; illustrated. United States Naval Institute, Annapolis, Maryland, 1960. Price $6.

CREATIVE VARIATION IN THE PROJECTIVE TECHNIQUES, by *Molly Harrower*, Ph.D., *Pauline Vorhaus*, Ed.D., *Melvin Roman*, Ph.D., and *Gerald Bauman*, Ph.D., with a foreword by Bruno Klopfer. 138 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $8.50.

DIFFERENTIAL DIAGNOSIS OF THE ELECTROCARDIOGRAM, by *Sidney R. Arbeit*, M.D., F.A.C.C., *Ira L. Rubin*, M.D., F.A.C.P., F.A.C.C. and *Harry Gross*, M.D., F.A.C.P. 212 pages; illustrated. F. A. Davis Co., Publisher, Philadelphia, Pa., 1960. Price $10.50.

PRACTICAL NURSE NUTRITION EDUCATION, by *Alberta Dent Shackelton*, B.S., M.S., M.Ed. 201 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa. Price $3.

ADAPTED PHYSICAL EDUCATION, by *Hollis F. Fait*, Ph.D. 332 pages; illustrated. W. B. Saunders Co. Philadelphia, Pa., 1960. Price $5.50.

CURRENT SURGICAL MANAGEMENT II, A Book of Alternative Viewpoints on Controversial Surgical Problems, edited by *John H. Mulholland*, M.D., *Edwin H. Ellison*, M.D., and *Stanley R. Friesen*, M.D., with 50 contributors. 348 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $8.

OFFICE DIAGNOSIS, by *Paul Williamson*, M.D. 470 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $12.50.

ORAL AND DENTAL DIAGNOSIS, with Suggestions for Treatment, by *Kurt H. Thoma*, D.M.D., Dr. med. dent. h.e., F.D.S.R.C.S. Eng., Hon. F.D.S.R.C.S. Edin., and *Hamilton B. G. Robinson*, D.D.S., M.S. 5th ed. 549 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $11.

THE RORSCHACH EXPERIMENT, Ventures in Blind Diagnosis, by *Samuel J. Beck*, Ph.D. 256 pages. Grune & Stratton, Inc., New York, N.Y., 1960. Price $6.50.

THE CHEMICAL SENSES IN HEALTH AND DISEASE, by *H. Kalmus*, Sc. D., M.D., and *S. J. Hubbard*, B. Sc., Ph.D. 95 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $3.75.

THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, A History, by *Zachary Cope*, Kt. 360 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1959. Price $13.50.

MEDICAL CARE OF THE ADOLESCENT, A Textbook Concerning the Medical Care and Understanding of Adolescents Themselves and of Their Disorders, by *J. Roswell Gallagher*, M.D., and the staff physicians of the Adolescent Unit, the Children's Hospital Medical Center, Boston, Mass. 369 pages; illustrated. Appleton-Century-Crofts, Inc., New York, N.Y., 1960. Price $10.

THE BIOCHEMICAL RESPONSE TO INJURY, A Symposium organized by The Council for International Organizations of Medical Sciences, established under the joint auspices of UNESCO and WHO, edited by *H. B. Stoner*, with the assistance of *C. J. Threlfall*. 467 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $12.50.

BLOOD PRESSURE SOUNDS AND THEIR MEANINGS. Part 2, Aetiology of Melanotic Cancer, by *John Erskine Malcolm*, M. Sc., M.B., Ch. B., F.R.C.S. 70 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $3.

EFFICIENCY OF HUMAN MOVEMENT, by *Marion R. Broer*, Ph. D. Photographs by *E. F. Marten*. 351 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $6.

GLAUCOMA, Transactions of the Fourth Conference, March 8, 9, and 10, 1959, Princeton, N.J., edited by *Frank W. Newell*, M.D. 257 pages; illustrated. Sponsored by the Josiah Macy, Jr. Foundation, New York, N.Y. Madison Printing Co., Inc., N.J., 1960. Price $8.

KINESIOLOGY, The Anatomic and Mechanical Fundamentals of Human Motion, by *Katharine F. Wells*, Ph. D. 3d edition. 515 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $5.75.

HISTOPLASMOSIS, edited by *Henry C. Sweany*, M.D. 538 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $14.50.

METAL-BINDING IN MEDICINE, Proceedings of a Symposium Sponsored by Hahnemann Medical College and Hospital, Philadelphia, Pa., edited by *Marvin J. Seven* and *L. Audrey Johnson*. 400 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $13.75.

ARTERIAL HYPERTENSION, by *Irvine H. Page*, M.D. 38 pages; illustrated. F. A. Davis Co., Publishers, Philadelphia, Pa., 1960. Price $2.

THE PHOTOGRAPHY OF PATIENTS, Including Discussions of Basic Photographic and Optical Principles and Infrared Techniques, by *Lou Gibson*, F.B.P.A., F.P.S.A. 2d edition. 200 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $10.50.

THE EGO IN LOVE AND SEXUALITY, by *Edrita Fried*, Ph. D. 296 pages. Grune & Stratton, New York, N.Y., 1960. Price $5.50.

CIBA FOUNDATION TENTH ANNIVERSARY SYMPOSIUM ON SIGNIFICANT TRENDS IN MEDICAL RESEARCH, edited by *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., M.R.C.P., *Cecilia M. O'Connor*, B.Sc., and *Maeve O'Connor*, B.A. 356 pages; illustrated. Little, Brown & Co., Boston, Mass., 1959. Price $9.50.

CLINICAL ENDOCRINOLOGY. I, edited by *Edwin B. Astwood*, M.D. 724 pages; illustrated. Grune & Stratton, New York, N.Y., 1960. Price $18.75.

VIRUS VIRULENCE AND PATHOGENICITY, in honour of Prof. *J. Mulder*. Ciba Foundation Study Group No. 4. Editors for the Ciba Foundation, *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., M.R.C.P., and *Cecilia M. O'Connor*, B. Sc. 114 pages; illustrated. Little, Brown & Co., Boston, Mass., 1960. Price $2.50.

CANCER OF THE CERVIX, Diagnosis of Early Forms, in honour of Prof. Dr. *C. Kaufmann*. Ciba Foundation Study Group No. 3. Editors for the Ciba Foundation, *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., M.R.C.P., and *Maeve O'Connor*, B.A. 114 pages; illustrated. Little, Brown & Co., Boston, Mass., 1959. Price $2.50.

FELLOWSHIP OF SURGEONS, A History of the American College of Surgeons, by *Loyal Davis*, M.D., F.A.C.S. 523 pages. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $10.50.

THE YEAR BOOK OF ORTHOPEDICS AND TRAUMATIC SURGERY (1959–1960 Year Book Series), edited by *Ralph K. Chormley*, M.D. (Deceased) and *H. Herman Young*, M.D., with a section on Plastic Surgery, edited by *Neal Owens*, M.D., F.A.C.S., F.I.C.S. 448 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $8.

THYMECTOMY FOR MYASTHENIA GRAVIS, A Record of Experiences at the Massachusetts General Hospital, by *Henry R. Viets*, M.D., and *Robert S. Schwab*, M.D. 143 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $7.

CLINICAL OBSTETRICS AND GYNECOLOGY, Vol. 3, No. 1. Obstetric Emergencies, edited by *Martin L. Stone*, M.D. Pediatric Gynecology, edited by *John W. Huffman*, M.D. 264 pages; illustrated. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York, N.Y., 1960. Price $18 per year.

SURGICAL GASTROENTEROLOGY, Considerations Based on Pathologic Physiology, by *Warner F. Bowers*, A.B., B. Sc., M.D., M. Sc., Ph. D. (Surg.). Medical illustrations by *George J. Thomas*, A.B., M. Med. Art. 498 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $18.50.

SURGERY OF REPAIR AS APPLIED TO HAND INJURIES, by *B. K. Rank*, C.M.G., M.S. (Melbourne), F.R.C.S. (England), F.R.A.C.S., and *A. R. Wakefield*, M.S. (Melbourne), F.R.C.S. (England), F.R.A.C.S., with a foreword by Sir *Gordon Gordon-Taylor*, K.B.E., C.B., LL.D., Sc. D., F.R.C.S., F.R.C.S. (Ed.), F.R.A.C.S., F.A.C.S., F.R.C.S. (Canada). 2d edition. 284 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $9.

OUTLINE OF ORTHOPAEDICS, by *John Crawford Adams*, M.D. (London), F.R.C.S. (England). 3d edition. 440 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $8.

MEDICAL PHYSICS, edited by *Otto Glasser*, Ph. D. Vol. III. 754 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $25.

ANATOMY, A Regional Study of Human Structure, by *Ernest Gardner*, M.D., *Donald J. Gray*, Ph. D., and *Ronan O'Rahilly*, M. Sc., M.D., illustrated by *Casper Henselmann*. 999 pages; illustrated. W. B. Saunders, Philadelphia, Pa., 1960. Price $15.

ANOREXIA NERVOSA, Its History, Psychology, and Biology, by *Eugene L. Bliss*, M.D., and *C. H. Hardin Branch*, M.D. 210 pages; illustrated. Paul B. Hoeber, Inc., Medical Division of Harper & Bros., New York, N.Y., 1960. Price $5.50.

PHYSIOLOGY OF PREMATURITY, Transactions of the Fourth Conference, March 25, 26, and 27, 1959, Princeton, N.J., edited by *Jonathan T. Lanman*, M.D. 187 pages; illustrated. Sponsored by the Josiah Macy, Jr., Foundation, New York, N.Y., 1960. Madison Printing Company, Inc., Madison, N.J., 1960. Price $4.50.

DERMATOLOGIC MEDICATIONS, by *Marguerite Rush Lerner*, M.D., and *Aaron Bunsen Lerner*, M.D., Ph. D. 2d edition. 208 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $6.

THE DYNAMICS OF PSYCHIATRIC DRUG THERAPY, edited by *G. J. Sarwer-Foner*, M.D., with a foreword by *D. E. Cameron*, M.D. 624 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $16.

CURRICULUM DEVELOPMENT, by *Amy Frances Brown*, R.N., B.Ed., M.S. in N., Ph. D. 851 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $10.

ESSENTIALS OF FLUID BALANCE, by *D. A. K. Black*, M.D., F.R.C.P. 2d edition. 135 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $4.50.

VERTEBRATE DISSECTION, by *Warren F. Walker, Jr.*, Ph. D. 2d edition. 340 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $4.25.

CLINICAL MANAGEMENT OF BEHAVIOR DISORDERS IN CHILDREN, by *Harry Bakwin*, M.D., and *Ruth Morris Bakwin*, M.D. 2d edition. 597 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $11.

SCIENCE AND PSYCHOANALYSIS. Vol. III, Psychoanalysis and Human Values, edited by *Jules H. Masserman*, M.D. 377 pages. Grune & Stratton, Inc., New York, N.Y., 1960. Price $11.

THE CLOWN FAMILY SPEECH BOOK (We Want Toto), by *Morris P. Pollock*, Ed.D., D.A.O., and *Miriam S. Pollock*, D.A.O. Illustrations by *Alice Freeman* and Dr. *Miriam Pollock*. 38 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $6.50.

THE HUMAN APOCRINE SWEAT GLAND IN HEALTH AND DISEASE, by *Harry J. Hurley*, M.D., D. Sc. (Med.), and *Walter B. Shelley*, M.D., Ph. D. 138 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $6.50.

DIABETES MELLITUS, A Handbook for Nurses, by *Marguerite M. Martin*, R.N. 167 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $3.50.

OSTEOCHONDRITIS DISSECANS, Loose Bodies in Joints, Etiology, Pathology, Treatment, by *I. S. Smillie*, O.B.E., Ch. M., F.R.C.S. (Ed.), F.R.F.P.S. 224 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $12.50.

THE CLINICAL SYNDROME OF DIABETES MELLITUS, by *John Lister*, M.A., M.D., M.R.C.P. (Lond.). 234 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1959. Price $4.50.

MYOCARDOSIS, Pathogenesis, Clinical Aspects and Therapy with Recent Investigations Concerning the Principles of Metabolic Electrocardiography, by *Ferdinand Wuhrmann*, M.D., with the collaboration of *Serge Niggli*, M.D., translated by *Harvey Adelson*, M.D. 218 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $10.50.

NAVAL LOGISTICS, by Vice Admiral *George C. Dyer*, U.S. Navy (Ret.). 351 pages; illustrated. United States Naval Institute, Annapolis, Md. George Banta Company, Inc., Menasha Wis., 1960. Price $5

MODERN PRACTICE IN CROWN AND BRIDGE PROSTHODONTICS, by *John F. Johnston*, D.D.S., F.A.C.D , *Ralph W. Phillips*, A.B., M.S., F.A.C.D., and *Roland W. Dykema*, D.D.S. 420 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $12.

PROFESSIONAL SCHOOL PSYCHOLOGY, edited by *Monroe G. Gottsegen*, Ph. D., and *Gloria B. Gottsegen*, M.A. 292 pages. Grune & Stratton, Inc., New York, N.Y., 1960. Price $7.75.

THE CHILD IN HOSPITAL, A Study of His Emotional and Social Well-Being, by *Hedley G. Dimock*. 236 pages. F. A. Davis Co., Publishers, Philadelphia, Pa., 1960. Price $4.50.

RECENT RESEARCH IN FREEZING & DRYING, edited by *A. S. Parkes*, C.B.E., F.R.S., and *Audrey U. Smith*, D. Sc., M.B., B.S. 320 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $13.75.

CRASH INJURIES, The Integrated Medical Aspects of Automobile Injuries and Deaths, by *Jacob Kulowski*, M.D., F.A.C.S., F.I.C.S. 1,080 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $32.50.

THE INTESTINAL TRACT, Structure, Function and Pathology in Terms of the Basic Sciences, by *Richard Paul Spencer*, A.B., M.A., M.D. 411 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $12.75.

AN INTRODUCTION TO EMBRYOLOGY, by *B. I. Balinsky*, Dr. Biol. Sc. 562 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $7.75.

THE YEAR BOOK OF DERMATOLOGY (1959–1960 Year Book Series), edited by *Rudolf L. Baer*, M.D., and *Victor H. Witten*, M.D. 479 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $9.

EDEMA, Mechanisms and Management; A Hahnemann Symposium on Salt and Water Retention, edited by *John H. Moyer*, M.D., and *Morton Fuchs*, M.D. 833 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $15.

CARCINOMA OF THE THYROID GLAND, A Clinical and Pathologic Study of 293 Patients at the University of California Hospital, by *Stuart Lindsay*, M.D. 168 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $8.50.

THE YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY (1959–1960 Year Book Series). Neurology, edited by *Roland P. Mackay*, M.D. Psychiatry, edited by *S. Bernard Wortis*, M.D. Neurosurgery, edited by *Oscar Sugar*, M.D. 640 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $9.

THE LYMPHOCYTE AND LYMPHOCYTIC TISSUE, by 21 authors, edited by *John W. Rebuck*, M.D., Ph. D. 312 pages; illustrated. Paul B. Hoeber, Inc., Medical Division of Harper & Bros., New York, N.Y., 1960. Price $10.50.

THRESHOLDS OF PROFESSIONAL NURSING PRACTICE, by *Frances M. McKenna*, R.N., M.A. 2d edition. 428 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $5.25.

FUNDAMENTALS OF CLINICAL HEMATOLOGY, by *Byrd S. Leavell*, M.D., and *Oscar A. Thorup, Jr.*, M.D. 503 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $10.

MEDICAL, SURGICAL, AND GYNECOLOGICAL COMPLICATIONS OF PREGNANCY, by the Staff of the Mount Sinai Hospital, New York, N.Y., edited by *Alan F. Guttmacher*, M.D., and *Joseph J. Rovinsky*, M.D. 619 pages; illustrated, Williams & Wilkins Co., Baltimore, Md., 1960. Price $16.50.

ADVANCES IN PEDIATRICS, edited by *S. Z. Levine*. Vol. XI, 1960. 285 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $8.

AN APPLICATION OF PSYCHOANALYSIS TO EDUCATION, by *Richard M. Jones*, Ph. D., with an introduction by *Lawrence S. Kubie*, M.D. 124 pages. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $5.50.

ELECTROCARDIOGRAPHIC TECHNIQUES, A Manual for Physicians, Nurses and Technicians, by *Kurt Schnitzer*, M.D. 2d revised and enlarged edition. 109 pages; illustrated. Grune & Stratton, Inc., New York, N.Y., 1960. Price $4.75.

PSYCHOANALYSIS AND MORAL VALUES, by *Heinz Hartmann*, M.D. 121 pages. International Universities Press, Inc., New York, N.Y., 1960. Price $3.

SIGMUND FREUD, His Exploration of the Mind of Man, by *Gregory Zilboorg*. 132 pages. Grove Press, Inc., New York, N.Y., 1960. Price $1.45.

NEUROCHEMISTRY OF EPILEPSY, Seizure Mechanisms and their Management, by *Donald B. Tower*, M.D., Ph.D. 335 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $9.

BASIC THEORY OF PSYCHOANALYSIS, by *Robert Waelder*. 273 pages. International Universities Press, Inc., New York, N.Y., 1960. Price $5.

POSTMORTEM HOMOGRAFTS, by *James Barrett Brown*, M.D., F.A.C.S., and *Minot P. Fryer*, M.D., F.A.C.S. 64 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $5.50.

A DICTIONARY FOR MEDICAL SECRETARIES, by *Isabel Alice Stanton*. 175 pages. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $6.50.

A PRIMER OF ELECTROCARDIOGRAPHY, by *George E. Burch*, M.D., F.A.C.P., and *Travis Winsor*, M.D., F.A.C.P. 4th edition, thoroughly revised. 293 pages; illustrated. Lea & Febiger, Philadelphia, Pa., 1960. Price $5.

THE SECRET SELF, Psychoanalytic Experiences in Life and Literature, by *Theodor Reik*. 329 pages. Grove Press, Inc., New York, N.Y., 1960. Price $2.45.

DYNAMICS IN PSYCHOLOGY, by *Wolfgang Kohler*. 158 pages; illustrated. Grove Press, Inc., New York, N.Y., 1960. Price $1.75.

ELECTROPHYSIOLOGY OF THE HEART, by *Brian F. Hoffman*, M.D., and *Paul F. Cranefield*, Ph.D., with a foreword by *Franklin D. Johnston*, M.D. 323 pages; illustrated. The Blakiston Division, McGraw-Hill Book Co., Inc., New York, N.Y., 1960. Price $12.50.

PEDIATRIC CLINICS OF NORTH AMERICA, Symposium on Recent Clinical Advances. Consulting editor, *Vincent C. Kelley*, M.D. Vol. 7, No. 2. 468 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. $15 per year (4 quarterly issues).

A SYMPOSIUM ON pH AND BLOOD GAS MEASUREMENT, Methods and Interpretation, edited by *Ronald F. Woolmer*, V.R.D., B.A., B.M., F.F.A.R.C.S., assisted by *Joy Parkinson*, B.A. 210 pages; illustrated. Little, Brown and Co., Boston, Mass., 1959. Price $8.50.

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